

FORM P-1390 (Modified)
(REV 11-2000)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

**TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371**

5941-01-DRK

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

10/009611

INTERNATIONAL APPLICATION NO.
PCT/US00/15071

INTERNATIONAL FILING DATE
31 May 2000

PRIORITY DATE CLAIMED
10 June 1999

TITLE OF INVENTION

METHOD OF INHIBITING AMYLOID PROTEIN AGGREGATION AND IMAGING AMYLOID DEPOSITS

APPLICANT(S) FOR DO/EO/US

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Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ has been communicated by the International Bureau.
 - c. ☒ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☐ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Published Specification, WO 00/76489

Express Mail No. EF378134357US

U.S. APPLICATION NO. (IF KNOWN) SEE 37 CFR 10/009611		INTERNATIONAL APPLICATION NO. PCT/US00/15071		ATTORNEY'S DOCKET NUMBER 5941-01-DRK	
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24. The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) : <input checked="" type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1040.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$890.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$740.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$710.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00 <div style="text-align: right;">ENTER APPROPRIATE BASIC FEE AMOUNT =</div>				CALCULATIONS PTO USE ONLY	
				\$1,040.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).				\$0.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	43 - 20 =	23	x \$18.00	\$414.00	
Independent claims	16 - 3 =	13	x \$84.00	\$1,092.00	
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>				\$0.00	
TOTAL OF ABOVE CALCULATIONS =				\$2,546.00	
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				\$0.00	
SUBTOTAL =				\$2,546.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).				\$0.00	
TOTAL NATIONAL FEE =				\$2,546.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable). <input type="checkbox"/>				\$0.00	
TOTAL FEES ENCLOSED =				\$2,546.00	
				Amount to be: refunded	\$
				charged	\$

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 23-0455 in the amount of \$2,546.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 23-0455. A duplicate copy of this sheet is enclosed.

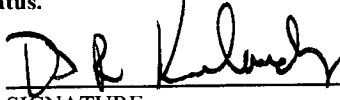
d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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NAME

41,505
REGISTRATION NUMBER

07 December 2001
DATE

METHOD OF INHIBITING AMYLOID PROTEIN AGGREGATION
AND IMAGING AMYLOID DEPOSITS

FIELD OF THE INVENTION

5 This invention relates to a method of inhibiting amyloid protein aggregation and imaging amyloid deposits. More particularly, this invention relates to a method of inhibiting amyloid protein aggregation in order to treat Alzheimer's disease.

BACKGROUND OF THE INVENTION

10 Amyloidosis is a condition characterized by the accumulation of various insoluble, fibrillar proteins in the tissues of a patient. The fibrillar proteins that comprise the accumulations or deposits are called amyloid proteins. While the particular proteins or peptides found in the deposits vary, the presence of fibrillar morphology and a large amount of β -sheet secondary structure is common to many types of amyloids. An amyloid deposit is formed by the aggregation of
15 amyloid proteins, followed by the further combination of aggregates and/or amyloid proteins.

The presence of amyloid deposits has been shown in various diseases, each with its particular associated protein, such as Mediterranean fever, Muckle-Wells syndrome, idiopathic myeloma, amyloid polyneuropathy, amyloid
20 cardiomyopathy, systemic senile amyloidosis, amyloid polyneuropathy, hereditary cerebral hemorrhage with amyloidosis, Alzheimer's disease, Down's syndrome, Scrapie, Creutzfeldt-Jacob disease, Kuru, Gerstmann-Straussler-Scheinker syndrome, medullary carcinoma of the thyroid, Isolated atrial amyloid, β_2 -microglobulin amyloid in dialysis patients, inclusion body myositis,
25 β_2 -amyloid deposits in muscle wasting disease, Sickle Cell Anemia, Parkinson's Disease, and Islets of Langerhans diabetes Type II insulinoma.

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Alzheimer's disease is a degenerative brain disorder characterized clinically by progressive loss of memory, cognition, reasoning, judgement, and emotional stability that gradually leads to mental deterioration and ultimately death. Because Alzheimer's disease and related degenerative brain disorders are a major medical issue for an increasingly aging population, the need for new treatments and methods for diagnosing the disorders are needed.

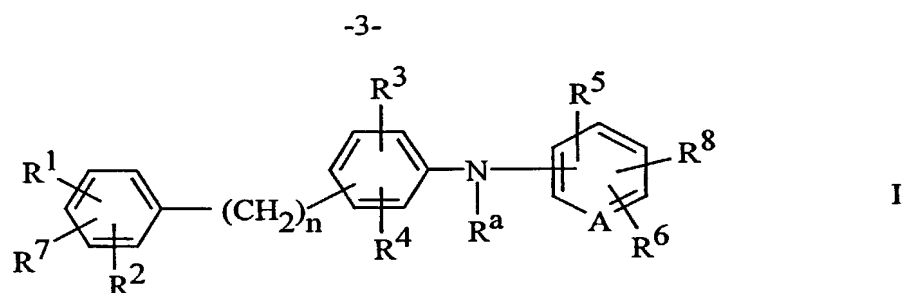
A simple, noninvasive method for detecting and quantitating amyloid deposits in a patient has been eagerly sought. Presently, detection of amyloid deposits involves histological analysis of biopsy or autopsy materials. Both methods have major drawbacks. For example, an autopsy can only be used for a postmortem diagnosis.

The direct imaging of amyloid deposits in vivo is difficult, as the deposits have many of the same physical properties (i.e., density and water content) as normal tissues. Attempts to image amyloid deposits directly using magnetic resonance imaging (MRI) and computer-assisted tomography (CAT) have been disappointing and have detected amyloid deposits only under certain favorable conditions. In addition, efforts to label amyloid deposits with antibodies, serum amyloid P protein, or other probe molecules has provided some selectivity on the periphery of tissues, but has provided for poor imaging of tissue interiors.

Thus, it would be useful to have a noninvasive technique for imaging and quantitating amyloid deposits in a patient. In addition, it would be useful to have compounds that inhibit the aggregation of amyloid proteins to form amyloid deposits.

SUMMARY OF THE INVENTION

The present invention provides a method of treating Alzheimer's disease, the method comprising administering to a patient having Alzheimer's disease a therapeutically effective amount of a compound of Formula I

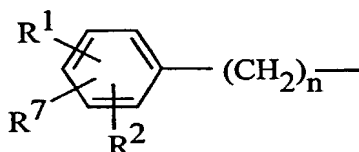


wherein

- 5 R^a is hydrogen, C_1 - C_6 alkyl, or $-CC_1$ - C_6 alkyl;
 n is 0 to 5 inclusive;
 R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 are independently hydrogen, halogen,
 $-OH$, $-NH_2$, NR^bR^c , $-CO_2H$, $-CO_2C_1$ - C_6 alkyl, $-NO_2$, $-OC_1$ - C_{12}
 $alkyl$, $-C_1$ - C_8 alkyl, $-CF_3$, $-CN$, $-OCH_2$ phenyl, $-OCH_2$ -substituted
10 phenyl, $-(CH_2)_m$ -phenyl, $-O$ -phenyl, $-O$ -substituted phenyl,
 $-CH=CH$ -phenyl, $-O(CH_2)_pNR^bR^c$, $-CNR^bR^c$, $-NHCR^b$,
 $-NH(CH_2)_pNR^bR^c$, $-N(C_1$ - C_6 alkyl) $(CH_2)_pNR^bR^c$,
15 $\begin{array}{c} \text{CH}_2OC_1-C_6 \text{ alkyl} \\ | \\ -CH \\ | \\ \text{CH}_2OC_1-C_6 \text{ alkyl} \end{array}$;
 R^8 is $COOH$, tetrazolyl, $-SO_2R^d$, or $-CONHSO_2R^d$;
 R^b and R^c are independently hydrogen, $-C_1$ - C_6 alkyl, $-(CH_2)_m$ -phenyl, or
 R^b and R^c taken together with the nitrogen atom to which they are
attached form a cyclic ring selected from piperidinyl, pyrrolyl,
20 imidazolyl, piperazinyl, 4- C_1 - C_6 alkylpiperazinyl, morpholino,
thiomorpholino, decahydroisoquinoline, or pyrazolyl;
 R^d is hydrogen, $-C_1$ - C_6 alkyl, $-CF_3$, or phenyl;
 m is 0 to 5 inclusive;
 p is 1 to 5 inclusive;
25 A is CH or N ;

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R^1 and R^2 , when adjacent to one another, can be methylene-dioxy;
or the pharmaceutically acceptable salts thereof.

In a preferred embodiment, the  group is attached at
the 4-position of the phenyl ring.

5 In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 2; and

R^3 and R^4 are hydrogen.

In a preferred embodiment of the method, in the compounds of Formula I

10 R^a is hydrogen;

R^1 is halo;

R^2 is hydrogen or halo;

R^3 , R^4 , R^5 , and R^6 are hydrogen; and

n is 2 to 5 inclusive.

15 In another preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 2 or 3;

R^1 is $-NR^bR^c$; and

R^2 , R^3 , R^4 , R^5 , and R^7 all are hydrogen.

20 In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

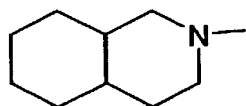
n is 2;

R^3 and R^4 are hydrogen; and

R^1 , R^2 , and R^7 are independently chlorine, $-N(CH_2CH_3)_2$, $-OH$, CH_3 -,

25 fluorine, $-CF_3$, phenyl, hydrogen, $-OCH_2$ phenyl,

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-O(CH₂)₃N(CH₃)₂, -O phenyl, -O(CH₂)₇CH₃,-CH(CH₂OCH₂CH₃)₂, pyrrolyl, -CH=CH-phenyl,, -N[(CH₂)₃CH₃]₂, substituted phenyl,-OCH₂-substituted phenyl, pyrrolyl, or -N(phenyl)₂.

5 In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 3, 4, or 5;

R³ and R⁴ are hydrogen; andR¹, R², and R⁷ are independently chlorine or hydrogen.

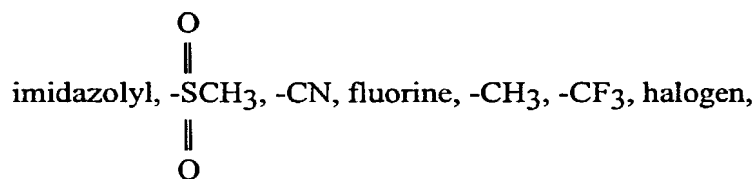
10 In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 2;

R³ and R⁴ are hydrogen; andR⁵, R⁶, and R⁸ are independently hydrogen, -CO₂H, -NO₂, -OCH₃,

15



20

-NH-C₁-C₆ alkyl, -N(C₁-C₆alkyl)₂, -NH₂, or pyrrolyl.

In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 2;

R³ and R⁴ are hydrogen; and

25

R⁵ is -CO₂H.

2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-
5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-
5-nitrobenzoic acid;

5 2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic
acid;

10 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-
5-nitrobenzoic acid;

2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

15 2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic
acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;

20 2-(4-Phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic
acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-benzoic

25 acid;

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methanesulfonyl-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-yl-
30 benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid;

- 5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-benzoic acid;
- 6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-benzoic acid;
- 2-{4-[2-(4-Benzoyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;
- 2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-phenylamino)-benzoic acid;
- 2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4'-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;

acid;

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2-{4-[2-(4-[2-Diethylaminoethylamino]phenyl)ethyl]phenylamino}-
benzoic acid;

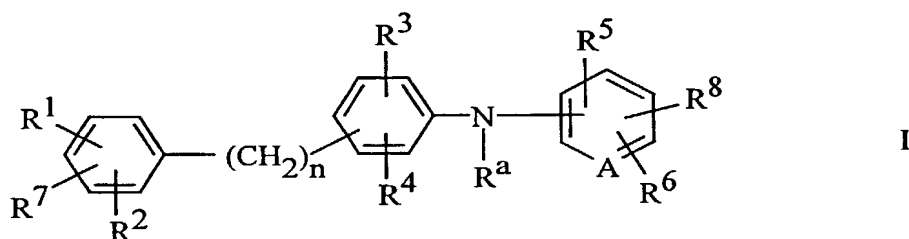
2-{4-[3-(4-Morpholinophenyl)propyl]phenylamino}-benzoic acid;

2-{4-[3-(4-Piperazinylphenyl)propyl]phenylamino}-benzoic acid; and

2-[4-(3,4-Dichlorophenyl)phenylamino]benzoic acid.

The invention also provides the foregoing compounds wherein the benzoic acid portion is replaced with a pyridyl carboxylic acid, for example, 4-[4-(3,4-dichlorophenyl)phenylamino]-3-hydroxycarbonylpyridine.

Also provided is a method of inhibiting the aggregation of amyloid proteins to form amyloid deposits, the method comprising administering to a patient in need of inhibition of the aggregation of amyloid protein an amyloid protein aggregation inhibiting amount of a compound of Formula I



wherein

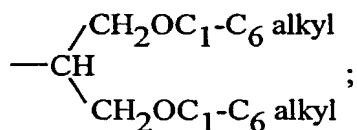
Ra is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, or $\text{-CC}_1\text{-C}_6$ alkyl;
 n is 0 to 5 inclusive;

$\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5, \text{R}^6$, and R^7 are independently hydrogen, halogen,

-OH , -NH_2 , NR^{bRc} , $\text{-CO}_2\text{H}$, $\text{-CO}_2\text{C}_1\text{-C}_6$ alkyl, -NO_2 , $\text{-OC}_1\text{-C}_{12}$ alkyl, $\text{-C}_1\text{-C}_8$ alkyl, -CF_3 , -CN , -OCH_2 phenyl, -OCH_2 -substituted phenyl, $\text{-(CH}_2\text{)}_m\text{-phenyl}$, -O-phenyl , $\text{-O-substituted phenyl}$,

-CH=CH-phenyl , $\text{-O(CH}_2\text{)}_p\text{NR}^{\text{bRc}}$, -CNR^{bRc} , -NHCR^{b} ,
 $\text{-NH(CH}_2\text{)}_p\text{NR}^{\text{bRc}}$, $\text{-N(C}_1\text{-C}_6\text{alkyl)(CH}_2\text{)}_p\text{NR}^{\text{bRc}}$,

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R⁸ is COOH, tetrazolyl, -SO₂R^d, or -CONHSO₂R^d;

R^b and R^c are independently hydrogen, -C₁-C₆ alkyl, -(CH₂)_m-phenyl, or

5

R^b and R^c taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl, imidazolyl, piperazinyl, 4-C₁-C₆ alkylpiperazinyl, morpholino, thiomorpholino, decahydroisoquinoline, or pyrazolyl;

R^d is hydrogen, -C₁-C₆ alkyl, -CF₃, or phenyl;

m is 0 to 5 inclusive;

10

p is 1 to 5 inclusive;

A is CH or N;

R¹ and R², when adjacent to one another, can be methylene-dioxy; or the pharmaceutically acceptable salts thereof.

In a preferred embodiment of the method, in the compounds of Formula I

15

R^a is hydrogen;

n is 2; and

R³ and R⁴ are hydrogen.

In a preferred embodiment of the method, in the compounds of Formula I

20

R^a is hydrogen;

R³ and R⁴ are hydrogen; and

n is 2 to 5 inclusive.

In a preferred embodiment of the method, in the compounds of Formula I

25

R^a is hydrogen;

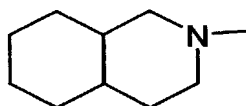
n is 2;

R³ and R⁴ are hydrogen; and

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R¹, R², and R⁷ are independently chlorine, -N(CH₂CH₃)₂, -OH, CH₃-,
fluorine, -CF₃, phenyl, hydrogen, -OCH₂ phenyl,
-O(CH₂)₃N(CH₃)₂, -O phenyl, -O(CH₂)₇CH₃,
-CH(CH₂OCH₂CH₃)₂, pyrrolyl, -CH=CH-phenyl,

5



, -N[(CH₂)₃CH₃]₂, substituted phenyl,

-OCH₂-substituted phenyl, pyrazolyl, or -N(phenyl)₂.

In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 3, 4, or 5;

10

R³ and R⁴ are hydrogen; and

R¹, R², and R⁷ are independently chlorine or hydrogen.

In a preferred embodiment of the method, in the compounds of Formula I

R^a is hydrogen;

n is 2;

15

R³ and R⁴ are hydrogen; and

R⁵ and R⁶ are independently hydrogen, -CO₂H, -NO₂, -OCH₃,

imidazolyl, -CN, fluorine, -CH₃, -CF₃, halogen,

-NH-C₁-C₆ alkyl, -N(C₁-C₆alkyl)₂, -NH₂, or pyrrolyl.

In a preferred embodiment of the method, in the compounds of Formula I

20

R^a is hydrogen;

n is 2;

R³ and R⁴ are hydrogen; and

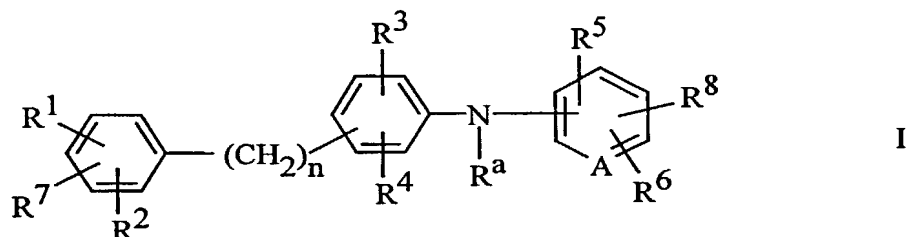
R⁵ is -CO₂H.

25

Also provided is a preferred method of inhibiting the aggregation of
amyloid proteins to form amyloid deposits, the method comprising administering

-14-

to a patient in need of inhibition of the aggregation of amyloid protein an amyloid protein aggregation inhibiting amount of a compound of Formula I



wherein

R^a is hydrogen;

n is 1 to 5 inclusive;

R^3 and R^4 are hydrogen;

R^1 , R^7 , and R^2 are independently chlorine, $-N(CH_2CH_3)_2$, $-OH$, CH_3 -,

fluorine, $-CF_3$, phenyl, hydrogen, $-OCH_2$ phenyl,

$-O(CH_2)_3N(CH_3)_2$, $-O$ phenyl, $-O(CH_2)_7CH_3$,

$-CH(CH_2OCH_2CH_3)_2$, pyrrolyl, $-CH=CH$ -phenyl,

$-N[(CH_2)_3CH_3]_2$, substituted phenyl, $-OCH_2$ -substituted phenyl,

pyrazolyl, or $-N(phenyl)_2$;

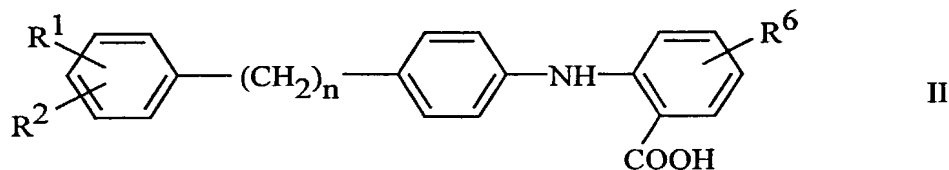
R^5 and R^6 are independently hydrogen, $-CO_2H$, $-NO_2$, $-OCH_3$,

imidazolyl, $-CN$, fluorine, $-CH_3$, $-CF_3$, or pyrrolyl;

R^8 is $COOH$ or tetrazolyl;

or the pharmaceutically acceptable salts thereof.

The most preferred compounds provided by the invention have Formula II



and pharmaceutically acceptable salts thereof,

wherein:

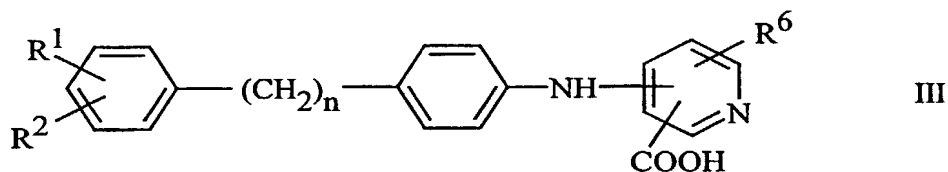
R^1 is halo;

R^2 is H or halo; and

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n and R⁶ are as defined above in Formula I.

Another preferred group of compounds have Formula III



and pharmaceutically acceptable salts thereof,

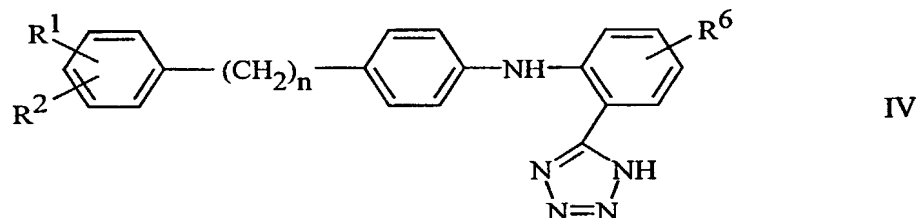
wherein:

R¹ is halo;

R² is H or halo; and

n and R⁶ are as defined above in Formula I.

Another group of preferred invention compounds have Formula IV



and pharmaceutically acceptable salts thereof,

wherein:

R¹ is halo;

R² is H or halo; and

n and R⁶ are as defined above in Formula I.

In a preferred embodiment of the method, the novel compounds of Formula I are provided which are

2-{4-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}benzoic acid;

- 2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic acid;
 2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-
 5-nitrobenzoic acid;
 2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-
 5-nitrobenzoic acid;
 2-{4-[2-[(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;
 2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid;
 2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-benzoic acid;
 2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic
 acid;
 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid;
 2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-
 5-nitrobenzoic acid;
 2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;
 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;
 2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;
 2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic
 acid;
 2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;
 5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;
 2-(4-Phenethyl-phenylamino)-benzoic acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic
 acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-benzoic
 acid;
 4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methanesulfonyl-
 benzoic acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-yl-
 benzoic acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-benzoic acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-benzoic acid;

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- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid;
 5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-benzoic
 acid;
 5 6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-benzoic
 acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-benzoic acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-benzoic acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-benzoic
 10 acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-benzoic acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-benzoic
 acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-
 15 benzoic acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-
 benzoic acid;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-
 benzoic acid;
 20 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-benzoic
 acid;
 2-{4-[2-(4-Benzyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-phenylamino)-
 benzoic acid;
 25 2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-
 phenylamino)-benzoic acid;
 30 2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

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- 2-{4-[2-(4'-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-benzoic
 acid;
 5 2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-phenylamino)-
 benzoic acid;
 2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-phenylamino)-
 10 benzoic acid;
 2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid;
 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl] phenylamino}-5-nitrobenzoic acid;
 2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-benzoic
 acid; or
 15 2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

The present invention also provides the compounds:

- 2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-
 5-nitrobenzoic acid;
 2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino} benzoic acid;
 20 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino} benzoic acid;
 2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino} benzoic acid;
 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-
 5-nitrobenzoic acid;
 25 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-
 5-nitrobenzoic acid;
 2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino} benzoic acid;
 2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-benzoic acid;
 2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic
 acid;
 30 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid;
 2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-
 5-nitrobenzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-benzoic acid;

- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-benzoic acid;
- 2-{4-[2-(4-Benzyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;
- 2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-phenylamino)-benzoic acid;
- 2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4'-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;
- 2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;
- 2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

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2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-phenylamino)-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-amino-benzoic
acid;

5 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-
benzoic acid;

2-{4-[2-(3,4-Dichlorophenyl)]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

10 2-{4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenylamino}-benzoic
acid;

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(4-Nitrophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(3-Nitrophenyl)propyl]phenylamino} benzoic acid;

15 2-{4-[3-(4-Aminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(3-Aminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[2-(4-Aminophenyl)ethyl]phenylamino} benzoic acid;

2-{4-[2-(4-Dipropylaminophenyl)ethyl]phenylamino} benzoic acid

monohydrochloride;

20 2-{4-[2-(4-Diethylaminophenyl)ethyl]phenylamino} benzoic acid
monohydrochloride monohydrate;

2-{4-[3-(3-Dipropylaminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(3-Dimethylaminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino} benzoic acid;

25 2-(N-{4-[3-(4-Diethylaminophenyl)propyl]phenyl}-N-ethylamino)benzoic
acid;

2-{4-[2-(3-Dibenzylaminophenyl)ethyl]phenylamino} benzoic acid;

2-{4-[3-(3-Diethylaminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[2-(3-Aminophenyl)ethyl]phenylamino} benzoic acid;

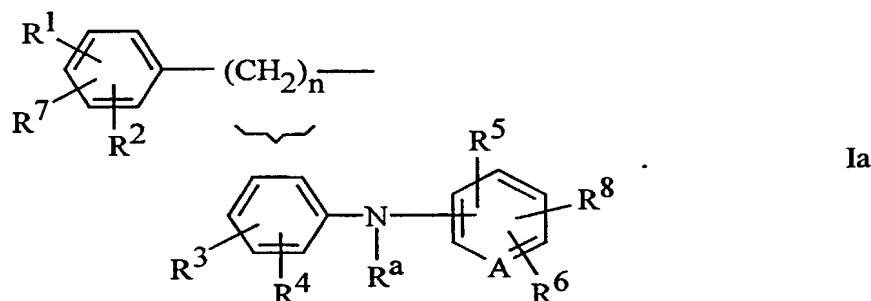
30 2-{4-[3-(4-Dimethylaminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[2-(4-Acetylaminophenyl)ethyl]phenylamino} benzoic acid;

2-{4-[2-(3-Acetylaminophenyl)ethyl]phenylamino} benzoic acid;

2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

Also provided are the foregoing compounds wherein the terminal phenylalkyl group is attached at the 2- or 3-position of the central phenyl ring, i.e., compounds of the Formula Ia



5 Typical 2- and 3-substituted compounds are:

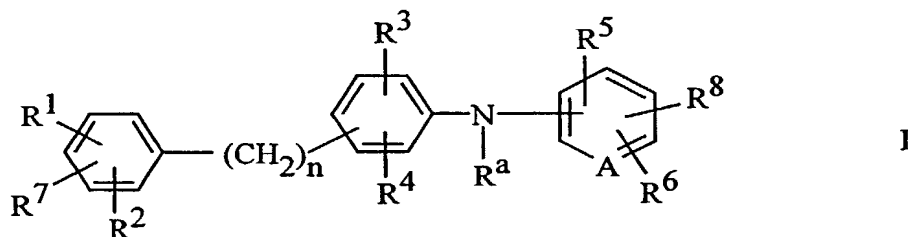
- 2-{3-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid;
- 2-{2-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid;
- 2-{3-[3-(4-Diethylaminophenyl)propyl]phenylamino}-benzoic acid;
- 2-{3-[3-(4-Di-n-propylaminophenyl)propyl]phenylamino}-benzoic acid;
- 10 2-{3-[3-(4-n-Propylaminophenyl)propyl]phenylamino}-benzoic acid;
- 2-{3-[3-(4-[2-Diethylaminoethylamino]phenyl)propyl]phenylamino}-benzoic acid;
- 2-{2-[3-(4-[Hydroxycarbonylmethylamino]phenyl)propyl]phenylamino}-benzoic acid;
- 15 2-{2-[2-(3-[2-Diethylaminoethylamino]phenyl)ethyl]phenylamino}-benzoic acid;
- 2-{3-[3-(4-Morpholinophenyl)propyl]phenylamino}-benzoic acid;
- 2-{3-[3-(4-Piperazinylphenyl)propyl]phenylamino}-benzoic acid;
- 2-{3-[2-(4-Chlorophenyl)ethyl]phenylamino}-benzoic acid;
- 20 2-{3-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-benzoic acid; and
- 2-{4-[4-(4-{4-Methylpiperazinyl}phenyl)butyl]phenylamino}-benzoic acid.

Pharmaceutical formulations of the novel compounds admixed with a pharmaceutically acceptable diluent, carrier, or excipient are also provided.

25 Also provided is a method of imaging amyloid deposits, the method comprising:

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- a. introducing into a patient a detectable quantity of a labeled compound having the Formula I or a pharmaceutically acceptable salt thereof:



wherein

R^a is hydrogen, C_1 - C_6 alkyl, or $-CC(=O)C_1$ - C_6 alkyl;

n is 0 to 5 inclusive;

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 are independently hydrogen,

halogen, -OH, -NH₂, NR^bR^c , -CO₂H, -CO₂ C_1 - C_6 alkyl, -NO₂, -OC₁- C_{12} alkyl, - C_1 - C_8 alkyl, -CF₃, -CN, -OCH₂ phenyl, -OCH₂-substituted phenyl, -(CH₂)_m-phenyl, -O-phenyl, -O-substituted phenyl,

-CH=CH-phenyl, -O(CH₂)_p NR^bR^c , -C(=O) NR^bR^c , -NHCR^b,
-NH(CH₂)_p NR^bR^c , -N(C_1 - C_6 alkyl)(CH₂)_p NR^bR^c ,

$\begin{array}{c} \text{CH}_2\text{OC}_1\text{-C}_6\text{ alkyl} \\ | \\ \text{---CH} \\ | \\ \text{CH}_2\text{OC}_1\text{-C}_6\text{ alkyl} \end{array}$;

R^8 is COOH, tetrazolyl, -SO₂ R^d , or -CONHSO₂ R^d ;

R^b and R^c are independently hydrogen, - C_1 - C_6 alkyl, -(CH₂)_m-phenyl, or R^b and R^c taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl, imidazolyl, piperazinyl, 4- C_1 - C_6

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alkylpiperazinyl, morpholino, thiomorpholino,
decahydroisoquinoline, or pyrazolyl;

R^d is hydrogen, -C₁-C₆ alkyl, -CF₃, or phenyl;

m is 0 to 5 inclusive;

5 p is 1 to 5 inclusive;

A is CH or N;

R¹ and R², when adjacent to one another, can be methylene-dioxy;
or the pharmaceutically acceptable salts thereof;

10 b. allowing sufficient time for the labeled compound to become
associated with amyloid deposits; and

c. detecting the labeled compound associated with the amyloid
deposits.

In a preferred embodiment of the method, the patient has or is suspected to have
Alzheimer's disease.

15 In a preferred embodiment of the method, the labeled compound is a radio labeled
compound.

In a preferred embodiment of the method, the labeled compound is detected using
MRI.

The present invention also provides the preferred compounds:

20 2-{4-[2-(3,4-Dichlorophenyl)ethyl]phenylamino}-benzoic acid;
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;
2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino} benzoic acid;
2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-benzoic
acid;
25 2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}-benzoic acid;
and pharmaceutical formulations thereof.

Pharmaceutically acceptable acid addition salts, amides, and prodrugs of the
foregoing compounds are also provided by this invention.

Substituent groups represented by R¹, R³, and R⁵, for example, include amino(NR^bR^c) and acylamino (-NHCOR^b). R^b and R^c can be hydrogen, alkyl and phenylalkyl and substituted phenylalkyl, and typical NR^bR^c groups include methylamino, diethylamino, isobutyl-propylamino, benzylamino, and 3,4-dimethoxybenzylamino. Examples of acylamino groups include formamido, acetamido, 2-phenylacetamido, and 2-(3-nitrophenyl)acetamido. R¹, R³, and R⁵ can also be aminoalkoxy (-O(CH₂)_pNR^bR^c) such as N-methylaminomethoxy and 2-(N-benzylamino)ethoxy, as well as

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aminoalkylamino ($-\text{NH}(\text{CH}_2)_p\text{NR}^b\text{R}^c$) such as 3-(dimethylamino)propylamino and 2-(N-ethyl-N-benzylamino)ethylamino. Substituent groups such as R^1 , R^3 , and R^5 additionally can be cyclic structures, for instance when NR^bR^c is part of the substituent group, and R^b and R^c are taken together with the nitrogen to which they are attached to form a cyclic ring selected from imidazole, pyrrole, piperidine, piperazine, 4- C_1 - C_6 alkylpiperazine, morpholine, thiomorpholine, pyrazole, and decahydroisoquinoline.

Substituent groups such as R^1 , R^2 , R^5 , R^6 , and R^7 also can be $-\text{CH}=\text{CH}$ -phenyl (i.e., styryl), phenoxy, O-substituted phenyl such as 3-iodophenoxy, 2,4,6-trihydroxyphenoxy, 2-fluoro-3-nitrophenoxy, as well as -O-benzyl and -O-substituted benzyl such as 2-trifluoromethylbenzyloxy and 4-aminobenzyloxy.

The term "pharmaceutically acceptable salt, ester, amide, and prodrug" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively nontoxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laureate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as, nontoxic ammonium, quaternary ammonium and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for

example, Berge S.M., et al., *Pharmaceutical Salts*, *J. Pharm. Sci.*, 66:1-19 (1977) which is incorporated herein by reference.)

Examples of pharmaceutically acceptable, nontoxic esters of the compounds of this invention include C₁-C₆ alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C₅-C₇ cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C₁-C₄ alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods, for example by reacting a carboxylic acid of Formula I with an alcohol such as ethanol or benzyl alcohol.

Examples of pharmaceutically acceptable, nontoxic amides of the compounds of this invention include amides derived from ammonia, primary C₁-C₆ alkyl amines and secondary C₁-C₆ dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines, the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C₁-C₃ alkyl primary amides and C₁-C₂ dialkyl secondary amides are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed in vivo to yield the parent compound of the above formulas, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

The compounds of the present invention can exist in different stereoisometric forms by virtue of the presence of asymmetric centers in the compounds. It is contemplated that all stereoisometric forms of the compounds, as well as mixture thereof, including racemic mixtures, form part of this invention.

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In the first step of the present method of imaging, a labeled compound of Formula I is introduced into a tissue or a patient in a detectable quantity. The compound is typically part of a pharmaceutical composition and is administered to the tissue or the patient by methods well-known to those skilled in the art.

5 In the methods of the present invention, a compound can be administered either orally, rectally, parenterally (intravenous, by intramuscularly or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments or drops), or as a buccal or nasal spray.

10 Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

15 These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

20 Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for

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example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates and sodium carbonate; (e) solution retarders, as for example paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft- and hard-filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

5 Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable nonirritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the
10 active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers or propellants as may be required. Ophthalmic formulations,
15 eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

In a preferred embodiment of the invention, the labeled compound is introduced into a patient in a detectable quantity and after sufficient time has passed for the compound to become associated with amyloid deposits, the labeled
20 compound is detected noninvasively inside the patient. In another embodiment of the invention, a labeled compound of Formula I is introduced into a patient, sufficient time is allowed for the compound to become associated with amyloid deposits, and then a sample of tissue from the patient is removed and the labeled compound in the tissue is detected apart from the patient. In a third embodiment
25 of the invention, a tissue sample is removed from a patient and a labeled compound of Formula I is introduced into the tissue sample. After a sufficient amount of time for the compound to become bound to amyloid deposits, the compound is detected.

The administration of the labeled compound to a patient can be by a
30 general or local administration route. For example, the labeled compound may be administered to the patient such that it is delivered throughout the body. Alternatively, the labeled compound can be administered to a specific organ or tissue of interest. For example, it is desirable to locate and quantitate amyloid

Another example of a suitable label in a compound of Formula I is an atom such as ^{13}C , ^{15}N , or ^{19}F which can be detected using magnetic resonance imaging (MRI) which is also sometimes called nuclear magnetic resonance (NMR). In addition, the labeled compounds of Formula I may also be detected by MRI using paramagnetic contrast agents.

Also provided by the present invention are compounds of Formula I wherein one or more atom in the compound has been replaced with a radioisotope (a labeled compound). The radioisotope can be any radioisotope. However, ^3H , ^{123}I , ^{125}I , ^{131}I , ^{11}C , and ^{18}F are preferred. Those skilled in the art are familiar with the procedure used to introduce a radioisotope into a compound. For example, a compound of Formula I wherein one carbon atom is ^{11}C or ^{14}C is readily prepared.

Scheme 9 depicts coupling of amine (VIII) with readily available methyl ester (XXVIII) in the presence of a base, such as imidazole, to give ester (XXIX).

This ester can then be saponified as usual to give compounds of Formula I.

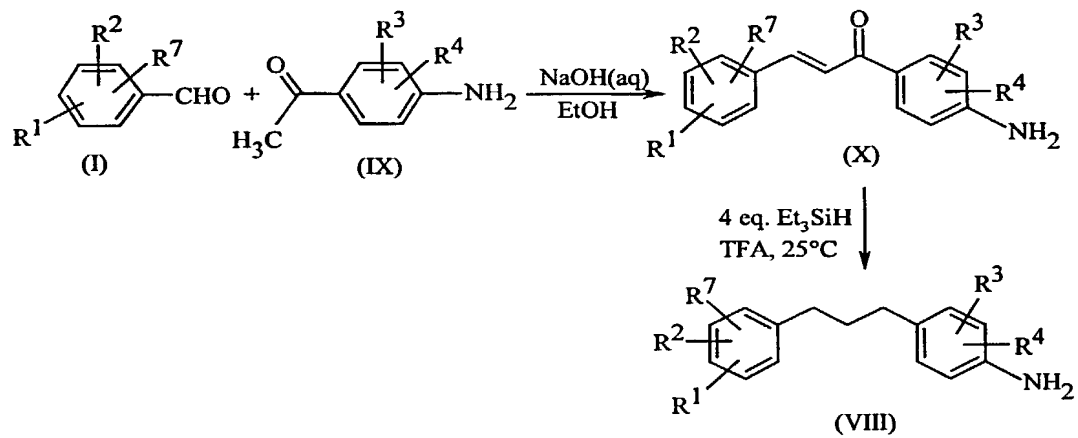
Scheme 10 illustrates the synthesis of fluoro-intermediate (XXIV) which is obtained by nitration of readily available methyl ester (XXX) to give (XXVIII). Treatment of (XXVIII) with potassium cyanide gives (XXIV).

5 In Scheme 11, the synthesis of compounds related to Example 18 is illustrated. Reaction of the potassium salts of ortho-substituted benzoic acids (XXVI) with substituted anilines (XXVII) in the presence of potassium carbonate and cupric acetate yields various iodo-substituted aminobenzoic acids (XXVIII). Reaction of (XXVIII) with substituted boronic acids and palladium chloride gives
10 the desired substituted aminobenzoic acids (XXX).

It should, of course, be recognized that several invention compounds of Formula I can be prepared from other compounds defined by Formula I, utilizing standard organic reactions such as oxidation, reduction, alkylation, condensation, elimination, and similar well-known synthetic processes. For example,

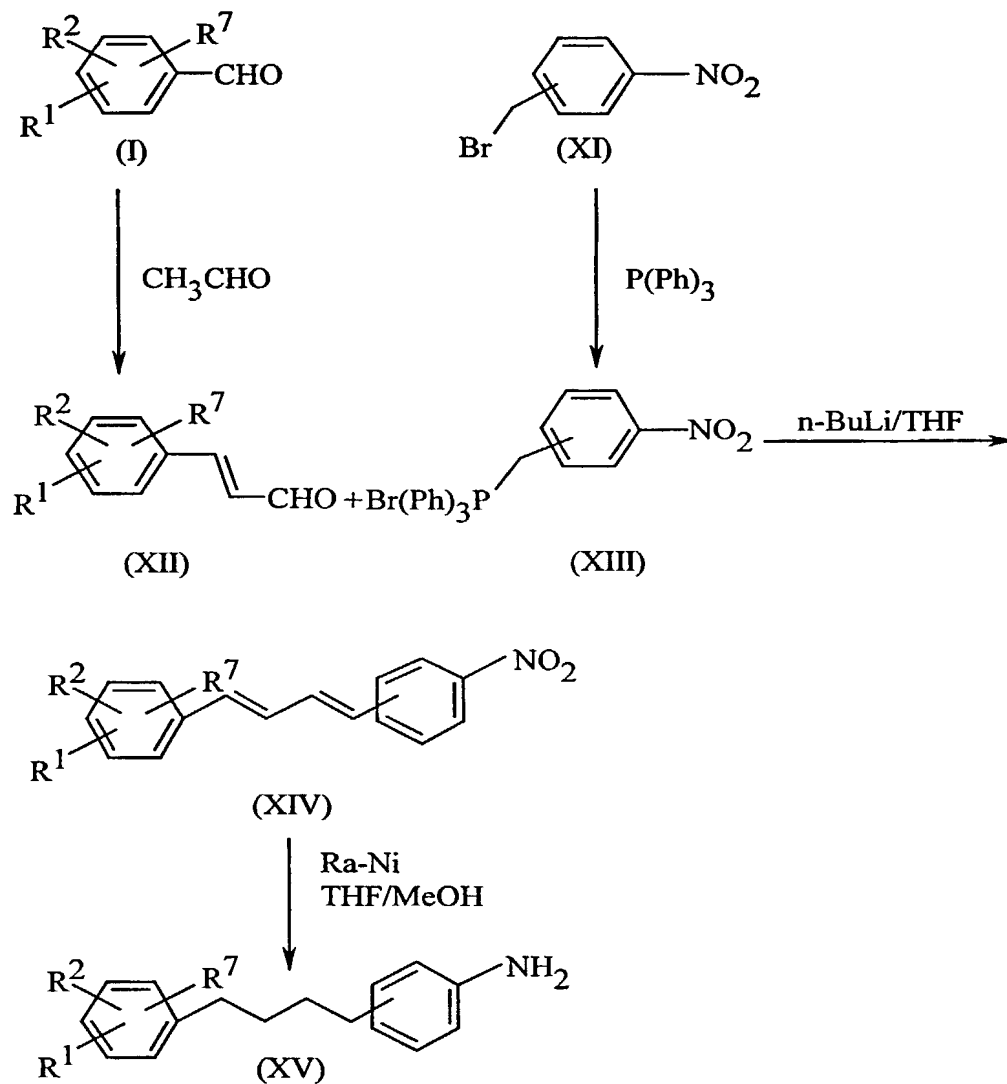
15 compounds of Formula I wherein R^a is hydrogen are readily alkylated to form compounds wherein R^a is C_1 - C_6 alkyl. Compounds wherein R^1 is NH_2 are readily acylated by reaction with an acid halide or acid anhydride to provide compounds wherein R^1 is $-NHCOR^b$. Similarly, compounds wherein R^1 is NO_2 are easily reduced to provide compounds wherein R^1 is NH_2 . The benzoic acids
20 (where R^8 is $COOH$) are readily converted to esters and amides, as well as salts and other prodrugs by routine processes. For example, the benzoic acid can be reacted with oxalylchloride to form the acid chloride, which then readily reacts with a sulfonamide such as methanesulfonamide to produce the corresponding invention compound where R^8 is $-CONHSO_2CH_3$.

Scheme 3



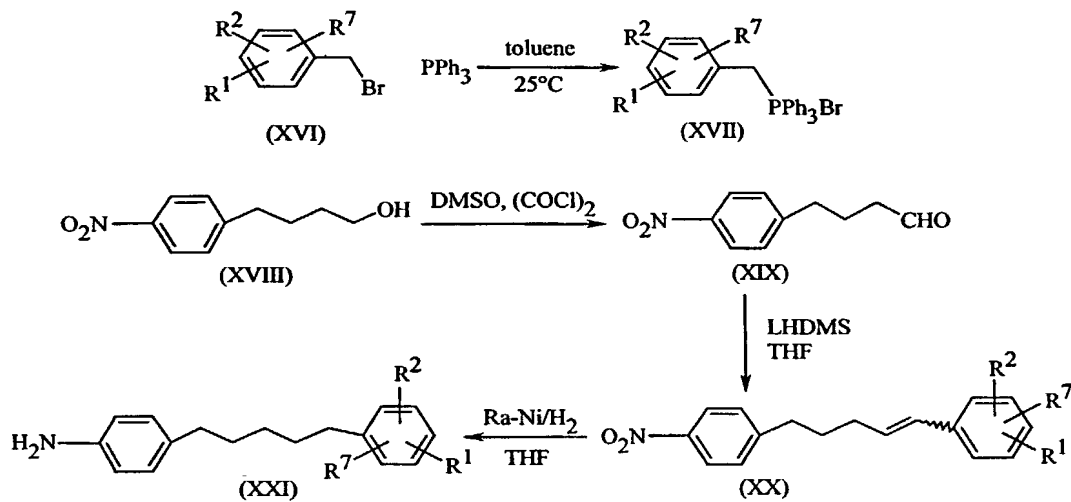
-39-

Scheme 4



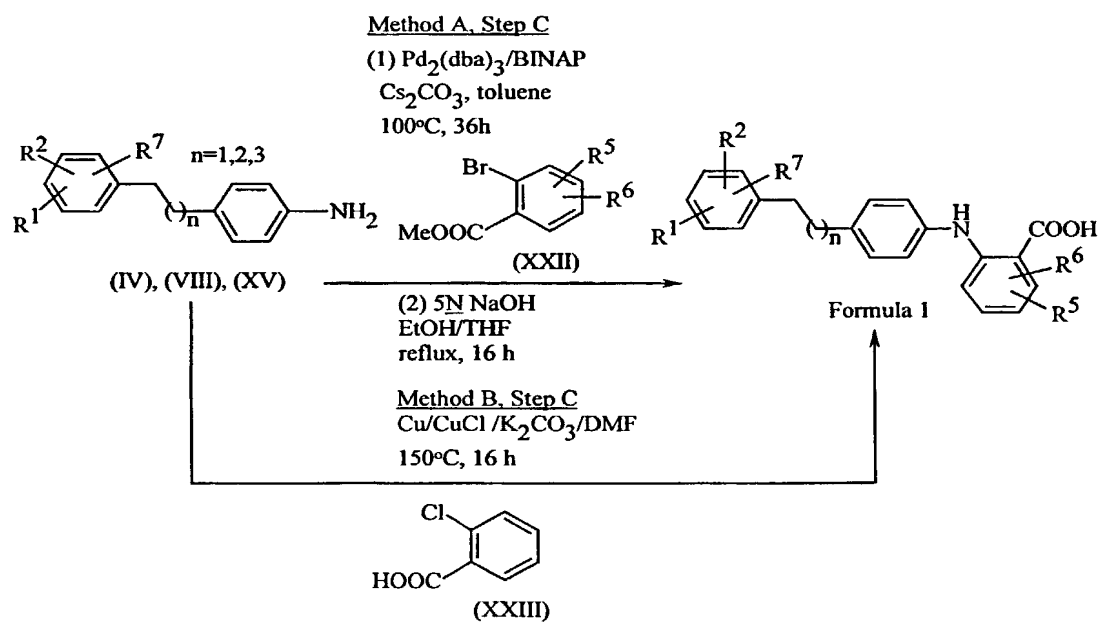
-40-

Scheme 5



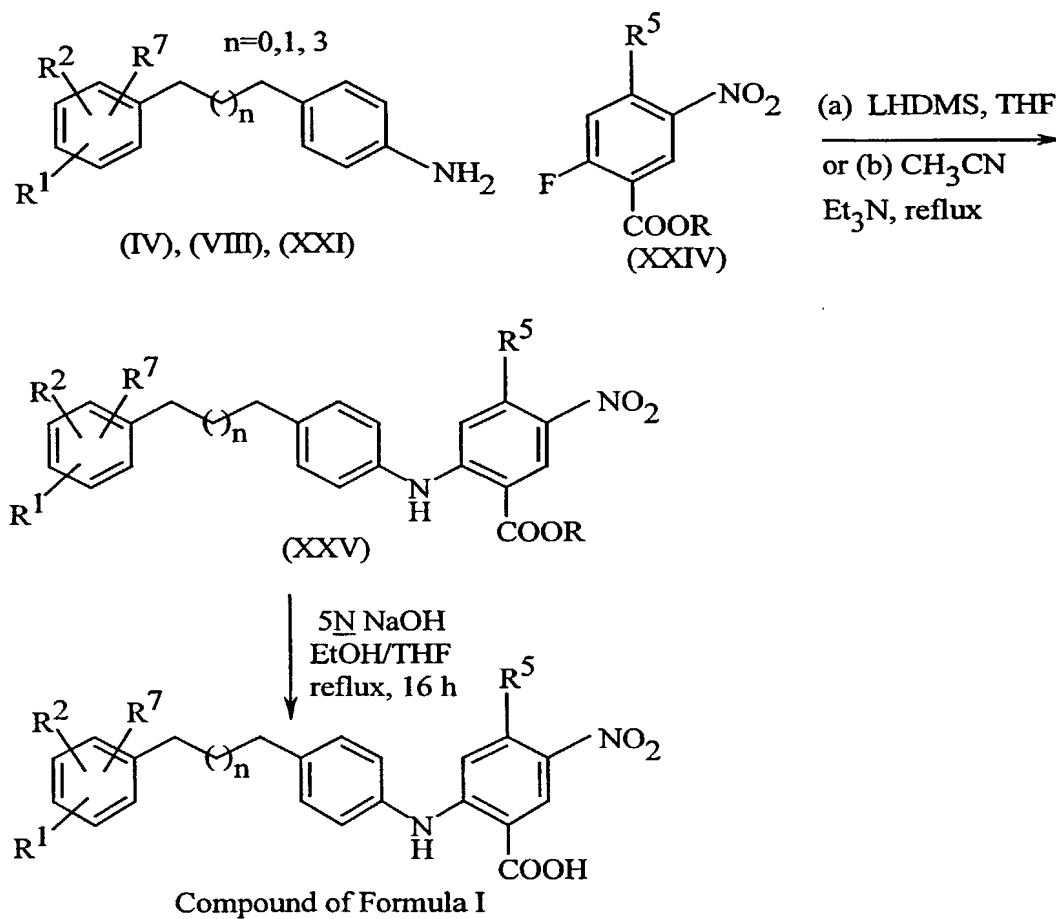
Coupling Routes

Scheme 6



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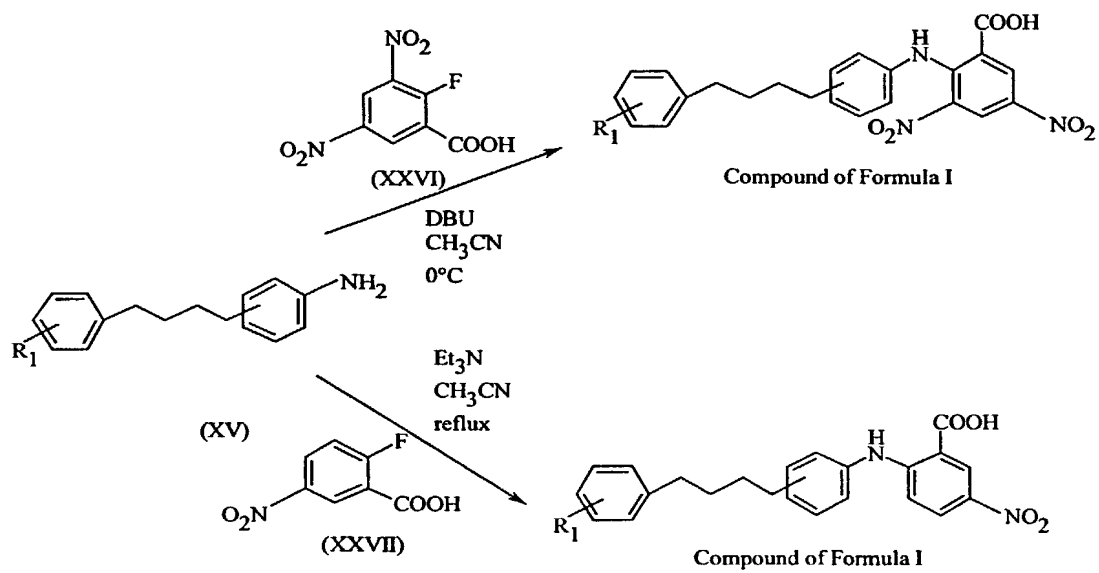
Scheme 7



R is an ester forming group such as alkyl or benzyl.

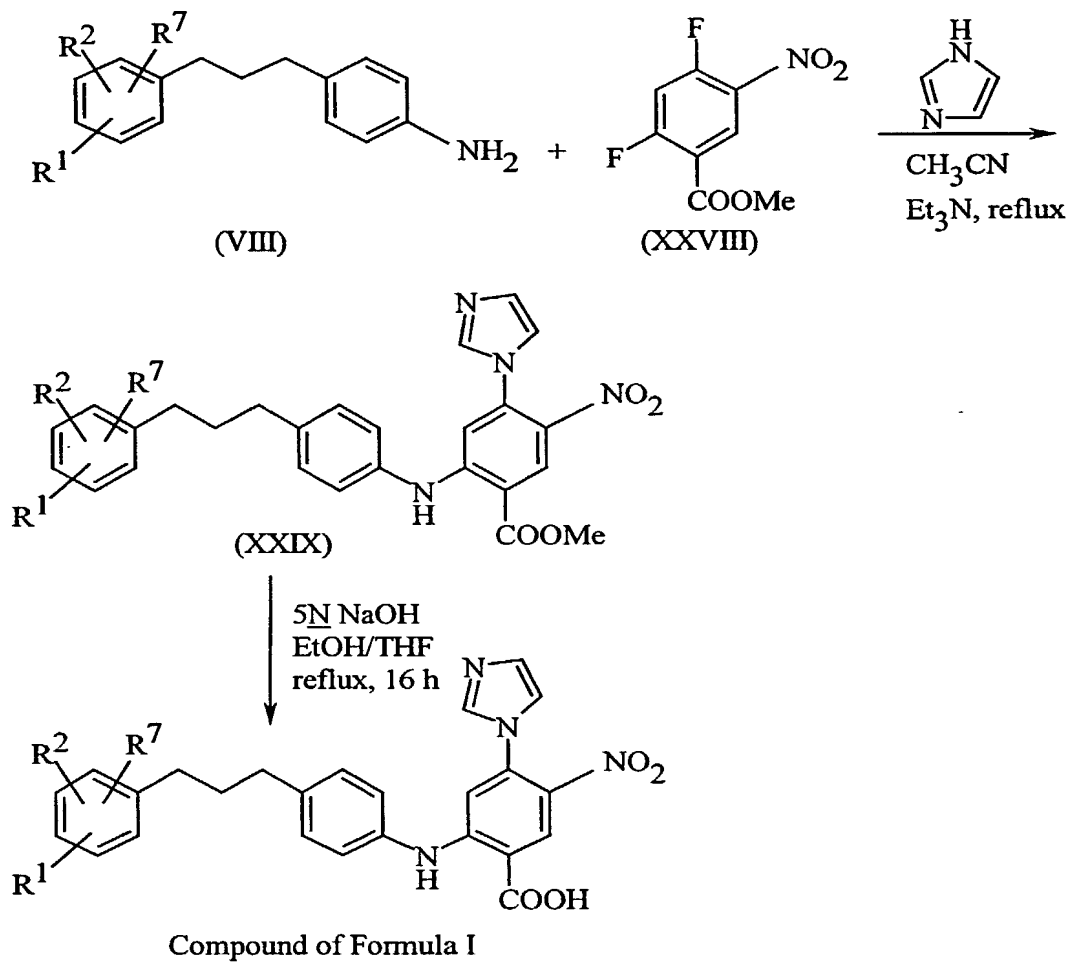
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Scheme 8



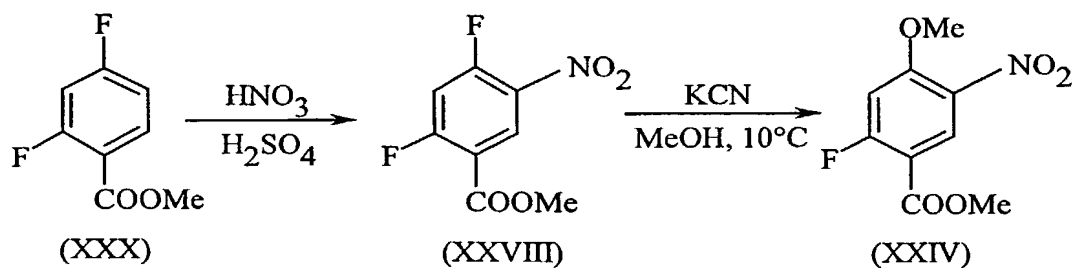
-43-

Scheme 9



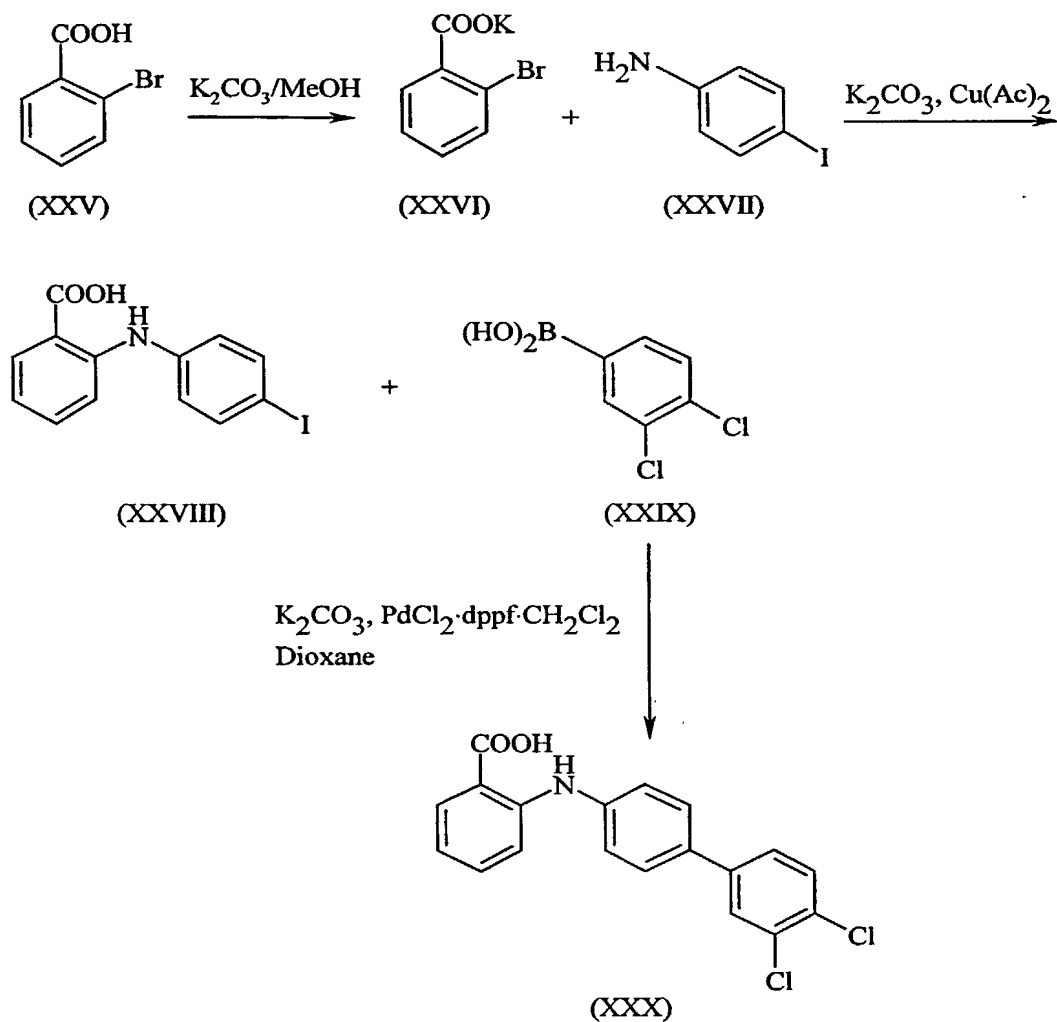
Synthesis of Fluoro-Intermediate

Scheme 10



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Scheme 11



25 A mixture of 4-[2-(3,4-dichlorophenyl)ethyl]benzenamine (28.37 g, 106.59 mmol), methyl 2-bromobenzoate (19.10 g, 88.82 mmol), cesium carbonate (40.52 g, 124.35 mmol), tris(dibenzylideneacetone-dipaladium(0) (2.44 g, 2.67 mmol) and (*S*)-(2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl (98%, (*S*)-tol-BINAP) (2.71 g, 4.00 mmol) (Ligand/Pd = 1.5) in anhydrous toluene (300 mL)

Found: C, 65.68; H, 4.58; N, 3.60.

EXAMPLE 2

Preparation of 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid

Step C (Scheme 6): Preparation of 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid methyl ester

A mixture of 4-[2-(3,4-dichlorophenyl)ethyl]benzenamine (600 mg, 2.25 mmol), 2-bromo-5-nitrobenzoic acid methyl ester (489 mg, 1.88 mmol), cesium carbonate (857 mg, 2.62 mmol), tris(dibenzylideneacetone-dipaladium(0) (51 mg, 0.056 mmol) and (*S*)-(2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl) (98%, (*S*)-tol-BINAP) (58 mg, 0.085 mmol) (Ligand/Pd = 1.5) in anhydrous toluene (16 mL) was heated to 100°C for 12 hours under N₂. After cooling, the reaction mixture was diluted with ether, filtered through celite and rinsed thoroughly with ether. The filtrate was evaporated to dryness to give a brown residue. Purification by flash chromatography (silica gel, 5% EtOAc/hexane) yielded 540 mg (1.21 mmol, 64%) of the desired product. mp 107-108°C.

Analysis for C₂₂H₁₈N₂Cl₂O₄: Calcd: C, 59.34; H, 4.07; N, 6.29.

Found: C, 59.03; H, 4.04; N, 5.99.

Preparation of 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid

A solution of 2-{4-[2-(3,4-dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid methyl ester (340 mg, 0.76 mmol) and 1N NaOH (aq.) (4.0 mL) in EtOH (4.0 mL) and THF (4.0 mL) was heated to reflux for 16 hours. The solvent was removed in vacuum. The residue was diluted with H₂O and acidified with concentrated HCl to pH 1. The mixture was then extracted with methylene chloride, dried (Na₂SO₄), filtered and concentrated in vacuo to yield a yellow solid, 329 mg (0.76 mmol, 100%) of the desired product. mp 214-217°C.

Analysis for C₂₁H₁₆N₂Cl₂O₄: Calcd: C, 58.49; H, 3.74; N, 6.50.

Found: C, 58.24; H, 3.81; N, 6.28.

Analysis of $C_{16}H_{15}N_1O_4$: Calcd: C, 67.36; H, 5.30; N, 4.91. Found: C, 66.81; H, 5.27; N, 4.84.

Step B (Scheme 1): Preparation of 4-[2-(3,4-Dimethoxy-phenyl)ethyl]-phenylamine

1,2-Dimethoxy-4-[2-(4-nitrophenyl)ethenyl]benzene (12.1 g, 0.042 mol) was reduced in the presence of 10% Pd-C (2.0 g) in dimethylformamide (DMF) (120 mL) at 25°C under a hydrogen atmosphere. The reaction mixture was concentrated in vacuo to give a solid. The solid was recrystallized from MeOH (400 mL) to yield a white crystalline product, 6.8 g (0.026 mol, 63%) of the desired product. mp 115-116°C.

Analysis for $C_{16}H_{19}N_1O_2$: Calcd: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.60; H, 7.39; N, 5.35.

Step C (Scheme 6): Preparation of 2-{4-[2-(3,4-Dimethoxy-phenyl)ethyl]-phenylamino}benzoic acid

The title compound was prepared from 4-[2-(3,4-dimethoxy-phenyl)-ethyl]phenylamine (9.25 g, 0.036 mol), 2-chlorobenzoic acid (5.2 g, 0.036 mol), anhydrous potassium carbonate (15.0 g, 0.11 mol), copper powder (0.45 g, 0.007 mol), and a catalytic amount of copper(I) chloride in dry DMF (75 mL) using the procedure described in Example 1, Step C, Method B. After crystallization with MeOH/H₂O, 4.5 g (0.012 mol, 33%) of the desired product was obtained. mp: 137-139°C.

Analysis for $C_{23}H_{23}N_1O_4$: Calcd: C, 73.19; H, 6.14; N, 3.71. Found: C, 73.47; H, 6.03; N, 3.78.

Step D: Preparation of 2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}-benzoic acid

To a solution of 2-{4-[2-(3,4-dimethoxy-phenyl)-ethyl]phenylamino}-benzoic acid (0.28 g, 0.74 mmol) in CH₂Cl₂ (20 mL), BBr₃ (3.5 mL, 1M in CH₂Cl₂, 3.5 mmol) was added at room temperature under a N₂ atmosphere. The reaction mixture was allowed to stir at room temperature for 2 hours and then poured into ice water (50 mL). This mixture was extracted with EtOAc, and the organic layer was washed two times with water, dried (Na₂SO₄), filtered and

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concentrated in vacuo to yield 0.24 g (0.69 mmol, 93%) of the desired product.
mp 215-217°C.

Analysis for $C_{21}H_{19}NO_4$: Calcd: C, 72.19; H, 5.48; N, 4.00. Found: C, 71.80;
H, 5.46; N, 3.99.

5

EXAMPLE 5

Preparation of 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}benzoic acid

Step A (Scheme 1): Preparation of 1,1-Dibutylamino-4-[2-(4-nitrophenyl)ethenyl]benzene

10 The title compound was prepared from *p*-nitrophenylacetic acid (9.92 g, 0.055 mol) and 4-dibutylamino-benzaldehyde (14.32 g, 0.055 mol) in piperidine (5 mL) using the procedure described in Example 1, Step A. This procedure yielded a red solid, 4.12 g (0.012 mol, 16%) of the desired product.

MS: 352.2. (M^+); 353.2. (MH^+).

15 Step B (Scheme 1): Preparation of 4-[2-(4,4-Dibutylaminophenyl)ethyl]-phenylamine

The title compound was prepared from 1,1-dibutylamino-4-[2-(4-nitrophenyl)ethenyl]benzene (4.10 g, 11.63 mmol) and Ra-Ni (2.0 g) in MeOH (100 mL) at 21°C to 32°C ($\Delta P = 3.6$ psi) under a hydrogen atmosphere using the procedure described in Example 1, Step B. This procedure yielded a colorless oil,
20 3.49 g (10.76 mmol, 92.6%) of the desired product.

MS: 325.3 (MH^+).

Step C (Scheme 6): Preparation of 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}-benzoic acid

25 The title compound was prepared from 2-chlorobenzoic acid (1.46 g, 9.36 mmol), 4-[2-(4,4-dibutylaminophenyl)ethyl]phenylamine (3.31 g, 10.20 mmol), anhydrous potassium carbonate (4.27 g, 30.88 mmol), copper powder (1.25 g, 19.65 mmol), and copper(I) chloride (0.092 g, 0.93 mmol) in dry DMF (30 mL) using the procedure described in Example 1, Step C, Method B.

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This procedure yielded a 0.39 g (0.87 mmol, 8.6%) of the desired product.

mp 115-117°C.

Analysis for $C_{29}H_{36}N_2O_2$: Calcd: C, 78.34; H, 8.16; N, 6.30. Found: C, 78.15; H, 8.07; N, 6.10.

5

EXAMPLE 6

Preparation of 2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic acid

Step A (Scheme 1): Preparation of 1,2,3-Trimethoxy-5-[2-(4-nitrophenyl)ethenyl]benzene

10

The title compound was prepared from *p*-nitrophenylacetic acid (18.6 g, 0.10 mol), 3,4,5-trimethoxy-benzaldehyde (19.6 g, 0.10 mol) and piperidine (5 mL) using the procedure described in Example 1, Step A. This procedure yielded a solid, 13.0 g (0.041 mol, 41%) of the desired product. mp: 192-195°C.

Step B (Scheme 1): Preparation of 4-[2-(3,4,5-Trimethoxy-phenyl)ethyl]-phenylamine

15

The title compound was prepared from 1,2,3-trimethoxy-5-[2-(4-nitrophenyl)ethenyl]benzene (9.5 g, 0.03 mol) and Ra-Ni (1.0 g) in THF (50 mL) at 21-26°C ($\Delta P = 9.6$ psi) under a hydrogen atmosphere using the procedure described in Example 1, Step B. This procedure yielded a tan powder, 6.6 g (0.023 mol, 74%) of the desired product. mp 91-93°C.

20

Step C (Scheme 6): Preparation of 2-{4-[2-(3,4,5-Trimethoxy-phenyl)-ethyl]phenylamino}-benzoic acid methyl ester

The title compound was prepared from 4-[2-(3,4,5-trimethoxyphenyl)-ethyl]phenylamine (0.75 g, 2.61 mmol), methyl 2-bromobenzoate (0.47 g, 2.17 mmol), cesium carbonate (0.99 g, 3.04 mmol), tris(dibenzylideneacetone-dipaladium(0) (0.06 g, 0.065 mmol) and (*S*)-(-0-2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl (98% (*S*)-Tol-BINAP) (0.066 g, 0.098 mmol) (Ligand/Pd = 1.5) in anhydrous toluene (100 mL) using the procedure described in Example 1, Step C, Method A to yield a yellow oil, 0.69 g (1.63 mmol, 76%) of the desired product.

25

25 Preparation of 2-{4-[2-[-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

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Step A' (Scheme 2): Preparation of 3-(3,4-Dichlorophenyl)-1-(4-nitro-phenyl)propenone

Sodium hydroxide (7.3 g, 0.18 mol) was dissolved in water (80 mL) and 95% EtOH (80 mL) and cooled to 10°C with an ice-H₂O bath.

5 3,4-Dichlorobenzaldehyde (31.8 g, 0.18 mol) was added in one portion. After the addition, the mixture was warmed to 15°C. 1-(4-Nitrophenyl)ethanone (30.0 g, 0.18 mol) was added at this temperature with rigorous stirring. After stirring for 5 minutes, the reaction mixture was diluted with 95% EtOH (300 mL). The resulting tan mixture was stirred at room temperature for 30 minutes, then stirred
10 with an ice-H₂O bath underneath the flask for 2 hours. The light brown solid was filtered off, washed with H₂O, and air-dried. The solid was dissolved in hot THF (1.5 L) and treated with charcoal. The resulting mixture was filtered off, and the filtrate was diluted with 95% EtOH (500 mL). This solution was filtered and oven-dried (40°C) to yield a light brown solid, 38.56 g (0.12 mol, 66%) of the title
15 compound. mp 220-223°C.

Analysis for C₁₅H₉Cl₂NO₃: Calcd: C, 55.93; H, 2.82; Cl, 22.01; N, 4.35.

Found: C, 55.79; H, 2.93; Cl, 22.16; N, 4.32.

Step B' (Scheme 2): Preparation of 1-(4-Amino-phenyl)-3-(3,4-dichlorophenyl)propan-1-one

20 3-(3,4-Dichlorophenyl)-1-(4-nitro-phenyl)propenone (34.56 g, 0.11 mol) was reduced in the presence of Ra-Ni (3.0 g) in THF (250 mL) at 20°C to 32°C (ΔP = 33.4 psi) under a hydrogen atmosphere. The reaction mixture was concentrated in vacuo and recrystallized from MeOH (100 mL) to give a light yellow solid, 23.5 g (0.080 mol, 75%) of the desired product. mp 127-129°C.

25 Analysis for C₁₅H₁₃Cl₂NO: Calcd: C, 61.24; H, 4.45; N, 4.76; Cl, 24.10.

Found: C, 60.91; H, 4.60; N, 4.70; Cl, 23.98.

Step C' (Scheme 2): Preparation of 4-[3-(3,4-Dichlorophenyl)propyl]phenylamine

A mixture of 1-(4-aminophenyl)-3-(3,4-dichlorophenyl)propan-1-one (20.0 g, 0.068 mol), NH₂NH₂-H₂O (16 mL), and KOH (85%, 5.6 g) in ethylene

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glycol (160 mL) was heated to reflux under a N₂ atmosphere for 16 hours. After cooling to room temperature, the reaction mixture was poured into ice-H₂O and extracted with CH₂Cl₂ (2 L). The layers were separated, and the organic layer was dried (Na₂SO₄) and concentrated in vacuo to afford an oil. Purification by
5 flash chromatography (silica gel, CH₂Cl₂) yielded an oil, 14.00 g (0.05 mol, 73%) of the desired product.

Analysis for C₁₅H₁₅Cl₂N: Calcd: C, 64.30; H, 5.40; N, 4.99; Cl, 25.31.

Found: C, 64.21; H, 5.59; N, 5.24; Cl, 24.87.

Preparation of 2,4-Difluoro-5-nitrobenzoic acid methyl ester

10 Fuming nitric acid 90% (8.5 mL, 0.19 mol) was added with gentle stirring to concentrated sulfuric acid 98% (125 mL) in a 1 L beaker. After stirring for 10 minutes at room temperature, 2,4-difluorobenzoic acid methyl ester (21.9 g, 0.127 mol) was added dropwise. After the addition, the reaction mixture was allowed to stir gently for 40 minutes at room temperature. The reaction mixture
15 was then poured into ice-H₂O (1 L) and stirred for 10 minutes. The mixture was extracted with EtOAc. The layers were separated, and the organic layer was washed sequentially with 1N NaCl, saturated NaHCO₃, H₂O and brine, dried (Na₂SO₄), filtered and concentrated in vacuo to afford a yellow residue. This residue was washed with 10% EtOAc/hexane, filtered, and dried to yield a pale
20 yellow solid, 29.0 g (0.133 mol, 82%). mp 78-80°C.

Analysis for C₈H₅F₂NO₄: Calcd: C, 44.25; H, 2.32; N, 6.45. Found: C, 44.18; H, 2.39; N, 6.14.

Preparation of 2-Fluoro-4-methoxy-5-nitrobenzoic acid methyl ester

25 A mixture of sodium metal (1.27 g, 0.055 mol) and MeOH (250 mL) was stirred at 0°C for 10 minutes. This solution was added to a solution of 2-fluoro-5-nitrobenzoic acid methyl ester (10.0 g, 0.046 mol) in MeOH (250 mL), and the mixture was stirred for 20 minutes at 0°C to 5°C. The reaction mixture was then allowed to warm to room temperature and stir for 2 hours. The mixture was then filtered to give an off-white precipitate. Recrystallization with CHCl₃ (70 mL)

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yielded an off-white crystalline solid, 1.825 g (0.008 mol, 17%) of the title compound.

Analysis for $C_9H_8F_1N_1O_5$: Calcd: C, 47.17; H, 3.52; N, 6.11. Found: C, 47.09; H, 3.47; N, 6.00.

5 Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid methyl ester

A mixture of 4-[3-(3,4-dichloro-phenyl)propyl]phenylamine (0.94 g, 3.3 mmol), 2-fluoro-4-methoxy-5-nitro-benzoic acid methyl ester (0.75 g, 3.3 mmol), and Et_3N (0.46 mL) in CH_3CN (30 mL) was heated to reflux for 10 120 hours. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic layer was dried (Na_2SO_4) and concentrated to give a solid. Recrystallization with MeOH yielded 0.67 g (1.37 mmol, 42%) of the desired product.

Analysis for $C_{24}H_{22}N_2Cl_2O_5 \cdot 0.42H_2O$: Calcd: C, 58.01; H, 4.63. N, 5.64; 15 Found: C, 57.61; H, 4.51; N, 5.94.

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

To a solution of 2-{4-[3-(3,4-dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid methyl ester (0.30 g, 0.061 mol) in THF (5 mL), 20 1N NaOH (aq.) (2.5 mL) was added, and the mixture was stirred for 36 hours at room temperature. The solvent was removed, and the residue was acidified with concentrated HCl to pH 3. The precipitate was collected by filtration and dried in vacuum for 16 hours. Recrystallization with MeOH gave the title compound as an orange solid 0.21 g (0.043 mol, 70%). mp 200-201°C.

Analysis for $C_{23}H_{20}N_2O_5Cl_2 \cdot 0.2H_2O$: Calcd: C, 57.68; H, 4.29; N, 5.85; 25 Cl, 14.81. Found: C, 57.71; H, 4.34; N, 5.58; Cl, 14.56.

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EXAMPLE 8

Preparation of 2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-
1-yl-5-nitrobenzoic acid

Preparation of 2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-
1-yl-5-nitrobenzoic acid methyl ester

A mixture of 2,4-difluoro-5-nitrobenzoic acid methyl ester (1.63 g, 7.5 mmol), imidazole (0.56 g, 8.25 mmol), and Et₃N (1.14 mL, 8.25 mmol) in CH₃CN (50 mL) was stirred for 16 hours at room temperature. To this deep orange solution, 4-[3-(3,4-dichlorophenyl)propyl]phenylamine (2.10 g, 7.5 mmol) and triethylamine (Et₃N) (1.14 mL, 8.25 mmol) was added, and the mixture was heated to reflux for overnight. The reaction mixture was cooled and concentrated in vacuo to afford a residue. This residue was diluted with CH₂Cl₂ and washed with a saturated K₂HCO₃ solution. The organic layer was dried (Na₂SO₄), filtered, and concentrated in vacuo to give a crude oil. Purification by flash chromatography (silica gel, 10% EtOAc/hexane) yielded 1.0 g (1.90 mmol, 25%) of the desired product.

MS: 524.1 (M⁺).

Preparation of 2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-
1-1-yl-5-nitrobenzoic acid

The title compound was prepared from 2-{4-[2-[(3,4-dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-5-nitrobenzoic acid methyl ester (1.0 g, 1.9 mmol), 1N NaOH (2.0 mL) in THF (30 mL) using the procedure described in Example 8. This procedure yielded an orange solid, 0.30 g (0.6 mmol, 32%) of the desired product.

Analysis for C₂₅H₂₀Cl₂N₄O₄·0.2H₂O: Calcd: C, 58.31; H, 3.99; N, 10.88; Cl, 13.89. Found: C, 58.34; H, 4.07; N, 10.73; Cl, 13.41.

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EXAMPLE 9

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}-benzoic acid

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-benzoic acid methyl ester

5 The title compound was prepared from 4-[3-(3,4-dichlorophenyl)propyl]-phenylamine (600 mg, 2.14 mmol), 2-bromobenzoic acid methyl ester (380 mg, 1.78 mmol), cesium carbonate (812 mg, 2.49 mmol), tris(dibenzylideneacetone-dipaladium(0) (49 mg, 0.053 mmol) and (*S*)-(2,2'-bis(di-*p*-tolylphosphino)-1,1'-binaphthyl (98%, (*S*)-tol-BINAP) (54 mg, 0.080 mmol) (Ligand/Pd = 1.5) in
10 anhydrous toluene (15 mL) using the procedure described in Example 2, Step C. This procedure yielded an yellow oil, 0.61 g (1.47 mmol, 69%) of the desired product.

MS: 414 (M^+), 416 (MH^+).

Analysis for $C_{23}H_{21}Cl_2O_2N \cdot 0.4 H_2O$: Calcd: C, 65.25; H, 5.23; N, 3.30.

15 Found: C, 65.76; H, 5.18; N, 3.10.

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-benzoic acid

 The title compound was prepared from 2-{4-[3-(3,4-dichlorophenyl)-propyl]phenylamino}benzoic acid methyl ester (0.41 g, 0.99 mmol), 1N NaOH (4.0 mL) in EtOH (4 mL) and THF (4 mL) using the procedure described in
20 Example 2. This procedure yielded a yellow solid, 0.32 g (0.80 mmol, 81%) of the desired product. mp 120-126°C.

Analysis for $C_{22}H_{19}Cl_2O_2N_1 \cdot 0.75 H_2O$: Calcd: C, 64.04; H, 5.00; N, 3.39.

Found: C, 64.17; H, 4.69; N, 3.18.

EXAMPLE 10

25 Preparation of 2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid

Preparation of (*trans*)-3-(3,4-Dichlorophenyl)-2-propenal

 A mixture of 3,4-dichlorobenzaldehyde (140.0 g, 0.8 mol) and acetaldehyde (300 mL) was cooled to 5°C. Potassium hydroxide (5.1 g, 0.091 mol) was dissolved in hot MeOH (40 mL), and the resulting solution was

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added to the above cooled mixture while maintaining the internal temperature at 25°C to 30°C. The mixture was allowed to stir in ice-H₂O bath for 40 minutes and then treated with acetic anhydride (400 mL). After the addition, the mixture was heated to 100°C with stirring for 30 minutes and then cooled to 30°C. To this mixture, 12N HCl/H₂O (102 mL/1.2 L) was added, and the resulting mixture was heated to reflux for 30 minutes and then cooled to room temperature. This heterogeneous mixture was filtered and washed with H₂O to afford a brown solid. The crude product was dissolved in EtOAc and washed with H₂O, dried (Na₂SO₄), and concentrated to dryness. Recrystallization from hexane/EtOAc (9:1) yielded 76.5 g (0.38 mol, 48%) of the title compound. mp: 91-93°C. Analysis for C₉H₆Cl₂O: Calcd: C, 53.77; H, 3.01; Cl, 35.27. Found: C, 53.75; H, 3.10; Cl, 35.58.

Preparation of (*trans*), (*trans*)-1,2-Dichloro-4-[4-(4-nitrophenyl)-1,3-butadienyl]benzene

A mixture of 4-nitro-benzyl bromide (200.0 g, 0.93 mol) and triphenylphosphine (244.0 g, 0.93 mol) in CHCl₃ (1.5 L) was heated to reflux for overnight. The reaction mixture was cooled to room temperature, concentrated in vacuo to remove CHCl₃ and then suspended in Et₂O and stirred rigorously. The suspension was filtered, and the off-white solid was washed with Et₂O, dried at 80°C for 16 hours to give 433.0 g (0.91 mol, 98%) of bromo[(4-nitrophenyl)methyl]triphenylphosphorane. A solution of bromo[(4-nitrophenyl)methyl]triphenylphosphorane (100.0 g, 0.23 mol) in dry THF (500 mL) was cooled to 5°C. n-Butyl lithium (n-BuLi) (2.4 M, 96 mL, 0.23 mol) was added dropwise to maintain the temperature between 5°C to 10°C. The cooling bath was then removed, and the reaction mixture was allowed to warm to room temperature. After 4 hours, a solution of (*trans*)-3-(3,4-dichlorophenyl)-2-propenal (36.2 g, 0.18 mol) in THF (100 mL) was added dropwise, and the resulting mixture was stirred at room temperature for 16 hours. The mixture was filtered, and the filtrate was concentrated in vacuo to give a residue. Purification

A mixture of 2-fluoro-5-nitrobenzoic acid (1.85 g, 0.01 mol), 4-[4-(3,4-dichlorophenyl)butyl]-phenylamine (2.94 g, 0.01 mol) and Et₃N (2.80 mL) in acetonitrile (110 mL) was heated to reflux for 48 hours. The reaction mixture was cooled and concentrated in vacuo to remove the solvent. The residue was dissolved in CH₂Cl₂ and washed with diluted HCl. The organic layer was dried (Na₂SO₄), concentrated in vacuo to give a crude solid. Purification by flash

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chromatography (silica gel, CH₂Cl₂) yielded 1.40 g (0.003 mol, 30%) of the desired product.

Analysis for C₂₃H₁₉N₂O₄Cl₂: Calcd: C, 60.27; H, 4.18; N, 6.11; Cl, 14.47.

Found: C, 60.16; H, 4.41; N, 6.09; Cl, 15.69.

5

EXAMPLE 12

Preparation of 2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic acid

To a cooled (0°C) solution of 4-[4-(3,4-dichlorophenyl)butyl]-phenylamine (1.47 g, 5.0 mmol) and DBU (0.75 mL, 7.5 mmol) in acetonitrile (25 mL), a solution of 2-fluoro-2,5-dinitrobenzoic acid (1.15 g, 5.0 mmol) in acetonitrile (15 mL) was added dropwise. After stirring for 30 minutes at 0°C, the reaction mixture was neutralized with dilute HCl and extracted with EtOAc, dried (Na₂SO₄), filtered and concentrated in vacuo to afford a crude residue.

Recrystallization with EtOH yielded a bright orange solid, 2.06 g (4.1 mmol, 82%) of the title compound.

Analysis for C₂₃H₁₉Cl₂N₃O₆: Calcd: C, 54.77; H, 3.80; N, 8.33; Cl, 14.06.

Found: C, 54.68; H, 4.00; N, 8.12; Cl, 13.81.

EXAMPLE 13

Preparation of 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid

Preparation of Bromo[(3,4-dichlorophenyl)methyl]triphenylphosphorane

A mixture of 4-bromomethyl-1,2-dichlorobenzene (2.40 g, 0.01 mol), and triphenylphosphine (5.24 g, 0.02 mol) in toluene (30 mL) was stirred for 16 hours at room temperature. The solid was filtered, rinsed with toluene, and oven-dried at room temperature to yield a white powder, 3.95 g (0.0078 mol, 78%) of the desired product.

¹H NMR [dimethylsulfoxide (DMSO):ppm] :7.89-7.61 (m, 15H), 7.50 (d, J=8.3 Hz, 1H), 7.04 (t, J=2.3 Hz, 1H), 6.97 (m, 1H), 5.20 (d, J=15.9 Hz, 2H).

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Preparation of 4-(4-Nitrophenyl)butyraldehyde

To a cooled solution (-70°C) of oxalyl chloride (2.0 M in CH₂Cl₂, 14.1 mL, 28.2 mmol), dimethylsulfoxide (DMSO) (4.40 g, 56.32 mmol) in CH₂Cl₂ (20 mL) was added dropwise. The resulting reaction mixture was then stirred for 30 minutes at -70°C under a nitrogen atmosphere. A solution of 4-(4-nitrophenyl)butan-1-ol (5.00 g, 25.6 mmol) in CH₂Cl₂ (3 mL) was added dropwise, and the reaction mixture was stirred for 1 hour at -70°C. Et₃N (16 mL, 115 mmol) was added, and the reaction mixture was then allowed to gradually warm to room temperature and stir for 30 minutes. The mixture was then quenched with H₂O and extracted with EtOAc. The organic layers were washed with 0.1N HCl solution, H₂O, brine, dried (Na₂SO₄), filtered, and concentrated in vacuo to give a lightly brown oil. Purification by flash chromatography (silica gel, 50% EtOAc/hexane) yielded 3.20 g (16.56 mmol, 65%) of the desired product.

¹H NMR (DMSO:ppm): 9.75 (s, 1H), 8.12 (d, *J*=8.3 Hz, 2H), 7.30 (d, *J*=8.3 Hz, 2H), 2.72 (t, *J*=7.7 Hz, 2H), 2.47 (t, *J*=7.1 Hz, 2H), 1.94 (m, 2H).

Preparation of 1,2-Dichloro-4-[5-(4-nitrophenyl)-1-pentenyl]benzene

A solution of bromo[(3,4-dichlorophenyl)methyl]triphenylphosphorane (3.95 g, 7.9 mmol) in dry THF (20 mL) was cooled to 0°C. LHDMS (1.0 M/THF, 9 mL, 9.0 mol) was added dropwise to maintain the temperature at 0°C. After stirring for 30 minutes, a solution of 4-(4-nitro-phenyl)butyraldehyde (1.45 g, 7.5 mmol) in THF (5 mL) was added dropwise, and the mixture was allowed to warm to room temperature within 2 hours. The mixture was then quenched with H₂O and extracted with EtOAc. The organic layers were washed with 0.1N HCl solution, H₂O, brine, dried (Na₂SO₄), filtered, and concentrated in vacuo to give a lightly brown oil. Purification by flash chromatography (silica gel, 10% EtOAc/hexane) yielded 2.5 g (7.4 mmol, 99%) of the desired product.

MS: 335 (M⁺), 337 (MH⁺).

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Preparation of 4-[5-(3,4-Dichlorophenyl)pentyl]phenylamine

The title compound was prepared from 1,2-dichloro-4-[5-(4-nitrophenyl)-1-pentenyl]benzene (2.5 g, 7.4 mmol), Ra-Ni (1 g) in THF (50 mL) at 25°C to 40°C ($\Delta P = 9.9$ psi) using the procedure described in Example 1, Step B. This procedure yielded 1.06 g (3.4 mmol, 46%) of the desired product.

^1H NMR (DMSO:ppm): 7.45 (d, $J=8.3$ Hz, 1H), 7.41 (d, $J=2.2$ Hz, 1H), 7.12 (m, 1H), 6.74 (d, $J=8.3$ Hz, 2H), 6.40 (d, $J=8.3$ Hz, 2H), 4.73 (s, 2H), 2.50 (t, $J=7.7$ Hz, 2H), 2.31 (t, $J=7.6$ Hz, 2H), 1.6-1.5 (m, 4H), 1.5-1.4 (m, 2H).

Preparation of 2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-5-nitrobenzoic acid

To a cooled (-78°C) solution of 4-[5-(3,4-dichlorophenyl)pentyl]phenylamine (0.231 g, 0.75 mmol) in THF (2 mL), LHDMS (2.25 mL, 1 M in hexane, 2.25 mmol) was added dropwise. The reaction mixture was allowed to stir at -78°C for 10 minutes. A solution of 2-fluoro-5-nitrobenzoic acid (0.139 g, 0.75 mmol) in THF (2 mL) was added dropwise, and this solution was stirred for 30 minutes at -78°C. The reaction mixture was allowed to gradually warm to room temperature and stir for 2 hours under N_2 atmosphere. The reaction mixture was diluted with EtOAc, and acidified with 1N HCl (pH 3). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to yield a brown residue.

Purification by flash chromatography (silica gel, 2% MeOH/ CH_2Cl_2) then recrystallization with MeOH yielded 265 mg (0.56 mmol, 75%) of the desired product. mp 147-148°C.

Analysis for $\text{C}_{24}\text{H}_{22}\text{Cl}_2\text{N}_2\text{O}_4 \cdot 0.37\text{H}_2\text{O}$: Calcd: C, 60.05; H, 4.77; N, 5.84.

Found: C, 59.67; H, 4.64; N, 5.51.

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EXAMPLE 14

Preparation of 2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

Preparation of 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid methyl ester

The title compound was prepared from 4-[5-(3,4-dichlorophenyl)pentyl]phenylamine (231 mg, 0.75 mmol), LHDMS (6.28 mL, 1 M in THF, 6.28 mmol) and 2-fluoro-4-methoxy-5-nitrobenzoic acid methyl ester (172 g, 0.75 mmol) in THF (5 mL) using the procedure described in Example 13.

Purification by flash chromatography (silica gel, 10% EtOAc/hexane) yielded 145 mg (0.28 mmol, 37%) of the desired product.

MS: 515.2 (M^+), 517.2 (MH^+).

Preparation of 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid

The title compound was prepared from 2-{4-[5-(3,4-dichlorophenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid methyl ester (145 mg, 0.28 mmol) and 1N NaOH (aq.) (0.56 mL) in THF (1.2 mL) using the procedure described in Example 2. Purification by flash chromatography (silica gel, 10% MeOH/ CH_2Cl_2), then recrystallization with MeOH yielded 58 mg (0.12 mmol, 41%) of the desired product. mp 192-193°C.

Analysis for $C_{25}H_{24}Cl_2N_2O_5$: Calcd: C, 59.65; H, 4.81; N, 5.56.

Found: C, 59.29; H, 4.58; N, 5.36.

EXAMPLE 15

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid

Preparation of 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid methyl ester

The title compound was prepared from 4-[3-(3,4-dichlorophenyl)propyl]phenylamine (420 mg, 1.50 mmol), 2-bromobenzoic acid methyl ester (310 mg,

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Analysis for $C_{24}H_{24}O_4N_2 \cdot 0.25 H_2O$: Calcd: C, 71.27; H, 5.98; N, 6.93.

Found: C, 70.48; H, 6.03; N, 6.85.

Preparation of 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid

5 The title compound was prepared 2-{4-[2-(3,4-dimethyl-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid methyl ester (1.12 g, 2.76 mmol), 1N NaOH (50 mL) in EtOH (50 mL) and THF (50 mL) using the procedure described in Example 2. This procedure yielded a yellow solid, 1.03 g (2.63 mmol, 81%) of the desired product. mp 214-216°C.

10 Analysis for $C_{23}H_{22}O_4N_2 \cdot 0.25 H_2O$: Calcd: C, 69.99; H, 5.74; N, 7.18.
Found: C, 69.90; H, 5.82; N, 6.81.

EXAMPLE 17

Preparation of 2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino]-benzoic acid

15 Step A (Scheme 1): Preparation of *trans*-1-Chloro-2-trifluoromethyl-4-[2-(4-nitrophenyl)ethenyl]benzene

 A mixture of p-nitrophenylacetic acid (51.85 g, 0.29 mol) and 4-chloro-3-trifluoromethylbenzaldehyde (47.85 g, 0.23 mol) in piperidine (19.5 g, 0.23 mol) was heated under N_2 atmosphere to 150°C to 160°C for 1 hour. The reaction
20 mixture was cooled to 80°C to 100°C and refluxing *i*-PrOH (150 mL) was added. The mixture was continued to cool to room temperature and then placed under refrigeration for 5 hours. The crystalline precipitate was filtered off, rinsed with cold *i*-PrOH, and dried at room temperature in a vacuum oven overnight to yield
25 *trans*-1-chloro-2-trifluoromethyl-4-[2-(4-nitrophenyl)ethenyl]benzene as an orange solid, 22.53 g (68.75 mmol, 30%). mp 173-174°C.

MS: 327.0 (M^+)

Step B (Scheme 1): Preparation of 4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]-benzenamine

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The title compound was prepared from *trans*-1-chloro-2-trifluoromethyl-4-[2-(4-nitrophenyl)ethenyl]benzene (22.53 g, 0.069 mol) and Ra-Ni (22 g) in THF (0.5 L) at 18°C to 29°C ($\Delta P = 20.5$ psi) under a hydrogen atmosphere using the procedure described in Example 1, Step B. This procedure yielded a white solid, 20.0 g (66.73 mmol, 97%) of the desired product. mp 62-64°C.

MS: 298.1 (M^+)

Preparation of 2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]-aminobenzoic acid

To a cold solution of 4-[2-(4-chloro-3-trifluoromethylphenyl)ethyl]-benzenamine (4.33 g, 14.45 mmol) in THF (50 mL) at -78°C, was added LHMDs (43.35 mL, 43.35 mmol) (1M/THF) dropwise. Allowed the reaction mixture to stir for 10 minutes at -78°C. A solution of 2-fluorobenzoic acid (2.02 g, 14.45 mmol) in THF (50 mL) was added dropwise. The mixture was stirred for 2 hours at -78°C, then warmed to room temperature and let stir for additional 3 hours. The reaction mixture was concentrated *in vacuo* (40°C) to remove the organic solvent. This residue was acidified to pH 3 with 3N HCl (aq.). This precipitate was collected by filtration, rinsed with 10% HCl (40 mL), and dried in vacuum for overnight to give as a pale solid, 4.3 g (10.24 mmol, 70%) of the desired product. mp 150-152°C.

Analysis for $C_{22}H_{17}O_2N_1ClF_3 \cdot 0.59 H_2O$: Calcd: C, 61.39; H, 4.26; N, 3.25.

Found: C, 61.01; H, 4.34; N, 3.30.

EXAMPLE 18

Preparation of 2-[4-(3,4-Dichlorophenyl)phenylamino]benzoic acid

Preparation of o-Bromobenzoic acid potassium salt

To a solution of o-bromobenzoic acid (201.03 g, 1.0 mol) in MeOH (500 mL), K_2CO_3 (69 g, 1.0 mol) was added. The mixture was concentrated to give the desired product (239.1 g, 1.0 mol, 100%).

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Preparation of 2-[(4-Iodophenyl)amino] benzoic acid

A mixture of o-bromobenzoic acid potassium salt (47.8 g, 0.2 mol), 4-iodoaniline (43.8 g, 0.2 mol), K_2CO_3 (13.8 g, 0.1 mol), and cupric acetate (2.87 g, 6%) in diglyme (100 mL) was heated to reflux for 30 minutes. The reaction mixture was diluted with H_2O (1.0 L) and filtered. The filtrate was acidified with diluted AcOH. The resulting precipitate was collected by filtration, washed with H_2O and dried in a vacuum at $50^\circ C$ for 16 hours. Recrystallization from EtOAc gave the desired product, a solid (29.7 g, 0.087 mol, 44%). mp $205-206^\circ C$.

Analysis for $C_{13}H_{10}N_1O_2I$: Calcd: C, 45.05; H, 2.97; N, 4.13. Found: C, 45.05; H, 2.97; N, 3.92.

Preparation of 2-[4-(3,4-Dichlorophenyl)phenylamino]benzoic acid

A mixture of 3,4-dichlorophenylboronic acid (880 mg, 2.3 mmol), 2-[(4-iodophenyl)amino]benzoic acid (339 mg, 1 mmol), $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ [1,1'-bis(diphenylphosphino)ferrocene palladium (II) chloride, complexed with dichloromethane (1:1)] (67 mg, 0.082 mmol), K_2CO_3 (829 mg, 6 mmol), and H_2O (2 mL) in dioxane (15 mL) was heated to reflux for 1 hour. The reaction mixture was diluted with EtOAc and filtered. The filtrate was treated with 1N HCl, washed with H_2O , brine, dried (Na_2SO_4), and concentrated in vacuum to give a yellow solid. Purification by flash chromatography (silica gel, 10% MeOH/ CH_2Cl_2) yielded 272 mg (0.76 mmol, 76%) of the desired product. mp $>220^\circ C$.

Analysis for $C_{19}H_{13}O_2N_1Cl_2$: Calcd: C, 63.23; H, 3.71; N, 3.88.

Found: C, 62.95; H, 3.73; N, 3.63.

By following the general procedures described above, the following additional invention compounds were prepared:

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EXAMPLE 19

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid

MS: 403 (M^+).Analysis for $C_{26}H_{30}N_2O_2 \cdot 0.40 \text{ mol H}_2\text{O}$: Calcd: C, 69.31; H, 6.87; N, 6.12.

5 Found: C, 69.29; H, 7.04; N, 6.35.

EXAMPLE 20

2-{4-[3-(4-Nitrophenyl)propyl]phenylamino}benzoic acid. mp 150-153°C.

MS: 376 (M^+).

EXAMPLE 21

10 2-{4-[3-(3-Nitrophenyl)propyl]phenylamino}benzoic acid. mp 164-167°C.

MS: 376 (M^+).Analysis for $C_{22}H_{20}N_2O_4 \cdot 2.20 \text{ mol H}_2\text{O}$: Calcd: C, 63.51; H, 5.91; N, 6.73.

Found: C, 63.56; H, 5.45; N, 6.46.

EXAMPLE 22

15 2-{4-[3-(4-Aminophenyl)propyl]phenylamino}benzoic acid. mp 110-112°C.

MS: 347 (M^{+1+}).

EXAMPLE 23

2-{4-[3-(3-Aminophenyl)propyl]phenylamino}benzoic acid. mp 109°C.

MS: 333 (M^{+1+}).

20

EXAMPLE 24

2-{4-[2-(4-Aminophenyl)phenylamino]benzoic acid. mp 198-201°C.

MS: 333 (M^{+1+}).Analysis for $C_{21}H_{20}N_2O_2 \cdot 0.1 \text{ mol H}_2\text{O}$: Calcd: C, 75.47; H, 6.09; N, 8.38.

Found: C, 75.32; H, 6.12; N, 8.27. Found: C, 75.32; H 6.12; N, 8.27.

MS: 375 ($M^{+}1^{+}$).

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Analysis for $C_{24}H_{26}N_2O_2 \cdot 0.1 H_2O$: Calcd: C, 76.61; H, 7.02; N, 7.44. Found: C, 76.62; H, 7.06; N, 7.36.

EXAMPLE 30

2-(N-{4-[3-(4-Diethylaminophenyl)propyl]phenyl}-N-ethylamino)benzoic acid

5 MS: 431 (M^{+1+}).

Analysis for $C_{28}H_{34}N_2O_2$: Calcd: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.02; H, 8.17; N, 6.50.

EXAMPLE 31

2-{4-[2-(3-Dibenzylaminophenyl)ethyl]phenylamino}benzoic acid.

10 mp 95.5-97.5°C.

Analysis for $C_{35}H_{32}N_2O_2$: Calcd: C, 82.00; H, 6.29; N, 5.46. Found: C, 81.81; H, 6.58; N, 5.44.

EXAMPLE 32

2-{4-[3-(3-Diethylaminophenyl)propyl]phenylamino}benzoic acid

15 MS: 403 (M^{+1+}).

Analysis for $C_{26}H_{30}N_2O_2 \cdot 0.1 H_2O$: Calcd: C, 77.23; H, 7.53; N, 6.93. Found: C, 77.14; H, 7.82; N, 6.88.

EXAMPLE 33

2-{4-[2-(3-Aminophenyl)ethyl]phenylamino}benzoic acid. mp 182-184°C.

20 MS: 333 (M^{+1+}).

Analysis for $C_{21}H_{20}N_2O_2 \cdot 0.25 H_2O$: Calcd: C, 74.87; H, 6.13; N, 8.43. Found: C, 74.86; H, 6.16; N, 8.32.

EXAMPLE 34

2-{4-[3-(4-Dimethylaminophenyl)propyl]phenylamino}benzoic acid

25 MS: 375 (M^{+1+}).

Analysis for $C_{24}H_{26}N_2O_2 \cdot 0.1 H_2O$: Calcd: C, 76.61; H, 7.02; N, 7.44. Found: C, 76.52; H, 7.22; N, 7.49.

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EXAMPLE 35

2-{4-[2-(4-Acetylaminophenyl)ethyl]phenylamino}benzoic acid. mp 224°C.

MS: 375 (M^{+1+}).

EXAMPLE 36

5 2-{4-[2-(3-Acetylaminophenyl)ethyl]phenylamino}benzoic acid. mp 213-215°C.

MS: 375 (M^{+1+}).

EXAMPLE 37

2-{4-[2-(3-Dipropylaminophenyl)ethyl]phenylamino}benzoic acid
monohydrochloride. mp 189-193°C.

10 MS: 417 (M^{+1+}).

Analysis for $C_{27}H_{32}N_2O_2 \cdot HCl$: Calcd: C, 71.58; H, 7.34; N, 6.18; Cl, 7.83.

Found: C, 71.48; H, 7.35; N, 6.10; Cl, 7.66.

EXAMPLE 38

2-{4-[2-(3-Dibutylaminophenyl)ethyl]phenylamino}benzoic acid
monohydrochloride. mp 175-180°C.

15

MS: 445 (M^{+}).

Analysis for $C_{29}H_{36}N_2O_2 \cdot HCl$: Calcd: C, 72.40; H, 7.75; N, 5.82; Cl, 7.37.

Found: C, 72.61; H, 7.95; N, 5.78; Cl, 7.23.

EXAMPLE 39

20 2-{4-[3-(4-Acetylaminophenyl)propyl]phenylamino}benzoic acid. mp 176-178°C.

MS: 389 (M^{+1+}).

EXAMPLE 40

2-{4-[3-(3-Acetylaminophenyl)propyl]phenylamino}benzoic acid. mp 140-145°C.

MS: 389 (M^{+1+}).

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EXAMPLE 41

2-{4-[2-(3-Diethylaminophenyl)ethyl]phenylamino}benzoic acid
monohydrochloride. mp 166-171°C.

MS: 389 (M^{+1+}).

- 5 Analysis for $C_{25}H_{28}N_2O_2 \cdot HCl$: Calcd: C, 70.66; H, 6.88; N, 6.59; Cl, 8.34.
Found: C, 70.48; H, 6.89; N, 6.57; Cl, 18.39.

EXAMPLE 42

2-{4-[2-(3-Piperidin-1-ylphenyl)ethyl]phenylamino}benzoic acid
monohydrochloride. mp 187-193°C.

- 10 MS: 401 (M^{+1+}).

Analysis for $C_{26}H_{28}N_2O_2 \cdot HCl$: Calcd: C, 71.46; H, 6.69; N, 6.41; Cl, 8.11.
Found: C, 71.28; H, 6.73; N, 6.35; Cl, 8.30.

EXAMPLE 43

2-{4-[3-(4-Dipropylaminophenyl)propyl]phenylamino}benzoic acid

- 15 MS: 431 (M^{+1+}).

Analysis for $C_{28}H_{34}N_2O_2$: Calcd: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.91;
H, 8.03; N, 6.43.

EXAMPLE 44

2-{4-[3-(4-Dibutylaminophenyl)propyl]phenylamino}benzoic acid

- 20 MS: 459 (M^{+1+}).

Analysis for $C_{30}H_{38}N_2O_2$: Calcd: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.40;
H, 8.50; N, 6.19.

EXAMPLE 45

2-{4-[3-(3-Dibutylaminophenyl)propyl]phenylamino}benzoic acid

- 25 MS: 459 (M^{+1+}).

Analysis for $C_{30}H_{38}N_2O_2$: Calcd: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.40;
H, 8.43; N, 6.11.

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EXAMPLE 46

2-(4-{3-[4-(1H-Pyrrol-1-yl)phenyl]propyl}phenylamino)benzoic acid.

mp 131-136°C.

MS: 397 (M^{+1+}).

5 Analysis for $C_{26}H_{24}N_2O_2 \cdot 0.2 H_2O$: Calcd: C, 78.05; H, 6.15; N, 7.00. Found: C, 77.95; H, 6.17; N, 7.08.

EXAMPLE 47

2-{4-[3-(4-Piperidin-1-yl)phenyl]propyl}phenylamino}benzoic acid

MS: 415 (M^{+1+}).

10 Analysis for $C_{27}H_{30}N_2O_2 \cdot 0.2 H_2O$: Calcd: C, 77.55; H, 7.33; N, 6.70. Found: C, 77.37; H, 7.35; N, 6.63.

EXAMPLE 48

2-{4-[3-(4-Diethylcarbamoylphenyl)propyl]phenylamino}benzoic acid.

mp 57-62°C.

15 MS: 431 (M^{+1+}).

Analysis for $C_{27}H_{30}N_2O_3 \cdot 0.3 H_2O$: Calcd: C, 74.39; H, 7.07; N, 6.43. Found: C, 74.23; H, 6.97; N, 6.27.

EXAMPLE 49

2-{4-[3-(4-Carboxyphenyl)propyl]phenylamino}benzoic acid. mp 236-239°C.

20 MS: 375 (M^{+}).

EXAMPLE 50

2-{4-[3-(4-Diethylaminomethylphenyl)propyl]phenylamino}benzoic acid.

mp 137°C.

MS: 417 (M^{+1+}).

25

EXAMPLE 51

2-{4-[3-(4-Propylaminophenyl)propyl]phenylamino}benzoic acid

MS: 389 (M^{+1+}).

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Analysis for $C_{25}H_{28}N_2O_2 \cdot 0.2 H_2O$: Calcd: C, 76.58; H, 7.30; N, 7.14. Found: C, 76.61; H, 7.29; N, 7.03.

EXAMPLE 52

2-{4-[3-(3-Propylaminophenyl)propyl]phenylamino}benzoic acid

5 MS: 389 (M^{+1+}).

Analysis for $C_{25}H_{28}N_2O_2 \cdot 0.1 H_2O$: Calcd: C, 76.93; H, 7.28; N, 7.18. Found: C, 76.85; H, 7.44; N, 7.06.

EXAMPLE 53

2-{4-[3-(4-Pyrrolidin-1-yl-phenyl)-propyl]-phenylamino}-benzoic acid.

10 mp 171-177°C.

MS: 401 (M^{+1+}).

Analysis for $C_{26}H_{28}N_2O_2 \cdot 0.2 H_2O$: Calcd: C, 77.27; H, 7.08; N, 6.93. Found: C, 77.09; H, 6.97; N, 6.96.

EXAMPLE 54

2-{4-[3-(3-Piperidin-1-yl-phenyl)-propyl]-phenylamino}-benzoic acid.

15 mp 59-61°C.

MS: 415 (M^{+1+}).

Analysis for $C_{27}H_{30}N_2O_2 \cdot 0.3 H_2O$: Calcd: C, 77.22; H, 7.34; N, 6.67. Found: C, 77.18; H, 7.25; N, 6.49.

EXAMPLE 55

{5-[(1-Butyl-1,2,3,4-tetrahydro-6-quinolyl)methylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid. mp 222-224°C.

20 MS: 391 (M^{+1+}).

EXAMPLE 56

{5-[(1-Butyl-2,3-dihydro-1H-indol-5-yl)methylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid. mp >250°C.

25 MS: 377 (M^{+1+}).

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Analysis for $C_{18}H_{20}N_2O_3S_2 \cdot 0.4 H_2O$: Calcd: C, 56.34; H, 5.46; N, 7.30; S, 16.71. Found: C, 56.27; H, 5.18; N, 7.31; S, 16.74.

EXAMPLE 57

3-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}propanoic acid. mp 214-215°C.

MS: 405 (M^{+1}).

EXAMPLE 58

4-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}butanoic acid. mp 152-154°C.

MS: 417 (M^{+1}), 418 (M^{+}), 419 (M^{+1}).

Analysis for $C_{21}H_{26}N_2O_3S_2 \cdot 0.2 H_2O$: Calcd: C, 59.74; H, 6.30; N, 6.64; S, 15.19. Found: C, 59.59; H, 6.16; N, 6.52; S, 15.38.

EXAMPLE 59

2-{4-[3-(3,4-Dichloro-phenyl)-propyl]phenylamino}-5-methyl-benzoic acid. mp 98-99°C.

MS: 414 (M^{+}).

EXAMPLE 60

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-methanesulfonamide was prepared by reacting the product from Example 9 with methanesulfonamide. mp 53-61°C.

Analysis for $C_{23}H_{22}Cl_2N_2O_3S \cdot 0.13 H_2O$: Calcd: C, 57.58; H, 4.68; N, 5.84. Found: C, 57.20; H, 4.66; N, 5.51.

EXAMPLE 61

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid. mp 214-216°C.

Analysis for $C_{23}H_{22}N_2O_4 \cdot 0.25 H_2O$: Calcd: C, 69.99; H, 5.74; N, 7.18. Found: C, 69.90; H, 5.82; N, 6.81.

Analysis for $C_{22}H_{17}F_4NO_2$: Calcd: C, 65.51; H, 4.25; N, 3.47. Found: C, 65.51; H, 4.13; N, 3.46.

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EXAMPLE 67

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid

mp 203-208°C.

Analysis for $C_{21}H_{16}F_2N_2O_4$: Calcd: C, 63.32; H, 4.05; N, 7.03.

5 Found: C, 62.94; H, 4.37; N, 6.87.

EXAMPLE 68

{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-[2-(1H-tetrazol-5-yl)-phenyl]-amine
was prepared as described in Example 1, using a tetrazole fluoro intermediate that
was synthesized from commercially available 2-fluorobenzonitrile and sodium
10 azide under standard reaction conditions. mp 129 shrink, 152-157°C.

Analysis for $C_{21}H_{17}Cl_2N_5 \cdot 0.15 \text{ EtOAc} \cdot 0.15 \text{ Hexane}$: Calcd: C, 61.80; H, 4.64;
N, 16.12. Found: C, 61.61; H, 4.28; N, 15.83.

EXAMPLE 69

2-{4-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic
15 acid. mp 190-193°C.

Analysis for $C_{22}H_{16}F_4N_2O_4$: Calcd: C, 58.93; H, 3.60; N, 6.25.

Found: C, 58.69; H, 3.42; N, 6.57.

EXAMPLE 70

2-(4-Phenethyl-phenylamino)-benzoic acid. mp 173-182°C.

20 Analysis for $C_{21}H_{19}NO_2$: Calcd: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.42;
H, 5.97; N, 4.47. Found: C, 79.59; H, 6.03; N, 4.50.

EXAMPLE 71

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-fluoro-benzoic acid.
mp 180-182°C.

25 Analysis for $C_{21}H_{16}Cl_2FNO_2 \cdot 0.06 \text{ H}_2\text{O}$: Calcd: C, 62.23; H, 4.01; N, 3.46.
Found: C, 61.83; H, 4.04; N, 3.29.

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EXAMPLE 72

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-nicotinic acid.

mp 168-171°C.

Analysis for $C_{20}H_{16}Cl_2N_2O_2$: Calcd: C, 62.03; H, 4.16; N, 7.23.

5 Found: C, 62.11; H, 4.17; N, 7.07.

EXAMPLE 73

2-{4-[2-(3-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.

mp 192.5-194.5°C.

Analysis for $C_{21}H_{17}ClN_2O_4$: Calcd: C, 63.56; H, 4.32; N, 7.06. Found: C, 63.83;

10 H, 4.62; N, 6.79.

EXAMPLE 74

2-{4-[2-(4-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.

mp 210-212°C.

Analysis for $C_{21}H_{17}ClN_2O_4 \cdot 0.26 H_2O$: Calcd: C, 62.82; H, 4.40; N, 6.98.

15 Found: C, 62.51; H, 4.34; N, 6.58.

EXAMPLE 75

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-benzoic acid.

mp 153-160°C.

Analysis for $C_{22}H_{19}Cl_2NO_2 \cdot 0.61 H_2O$: Calcd: C, 64.25; H, 4.96; N, 3.41.

20 Found: C, 63.87; H, 4.64; N, 3.55.

EXAMPLE 76

2-{4-[2-(2-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.

mp 236-238°C.

EXAMPLE 77

25 2-{4-[2-(2,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.

mp 200.5-202.5°C.

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Analysis for $C_{21}H_{16}Cl_2N_2O_4$: Calcd: C, 58.49; H, 3.74; N, 6.50.

Found: C, 58.33; H, 3.67; N, 6.29.

EXAMPLE 78

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-trifluoromethyl-benzoic
5 acid. mp 130-132°C.

Analysis for $C_{22}H_{16}Cl_2F_3NO_2$: Calcd: C, 58.17; H, 3.55; N, 3.08.

Found: C, 58.25; H, 3.65; N, 3.05.

EXAMPLE 79

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid.
10 mp >260°C.

EXAMPLE 80

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-dimethylamino-benzoic
acid. mp 75-80°C.

EXAMPLE 81

2-{4-[2-(3,5-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid. mp 191-194°C.

Analysis for $C_{21}H_{17}Cl_2NO_2$: Calcd: C, 65.30; H, 4.44; N, 3.63. Found: C, 65.38;
H, 4.29; N, 3.52.

EXAMPLE 82

2-(4-{2-[(4aS,8aR)-4-(Octahydro-isoquinolin-2-yl)-phenyl]-ethyl}-phenylamino)-
20 benzoic acid was prepared according to Example 1 using a decahydroisoquinoline
aldehyde which was prepared from trans-decahydroisoquinoline and para-
fluorobenzaldehyde under standard reaction conditions. mp 203-206°C.

Analysis for $C_{30}H_{34}N_2O_2 \cdot 0.12 H_2O$: Calcd: C, 78.89; H, 7.56; N, 6.13.

Found: C, 78.49; H, 7.58; N, 5.90.

25 The following examples are prepared according to the foregoing methods,
or by utilizing standard combinatorial synthetic methodology by reacting halo
substituted benzoate esters with a substituted aniline to form the corresponding

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diarylamine, followed by saponification to the benzoic acid of Formula I. The reactions are carried out on 0.15 mmol scale as follows. Solutions of each halo benzoate reactant (0.18 M) in toluene are placed in 2 dram reaction vials. Each aniline reactant is dissolved in anhydrous toluene to give 0.15 M solutions. A

5 Distriman pipet is used to add 1 mL (0.15 mmol, 1 eq) of each halo benzoate solution to the appropriate vials containing 1 mL (0.18 mmol, 1.2 eq) of the aniline reactants. A catalyst solution is prepared by dissolving 0.025 M of $\text{Pd}_2(\text{dba})_3$ (dipalladium-tridibenzylidene acetone) and 0.075 M of BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) in toluene, and 0.25 mL of the catalyst

10 solution is added to each reaction vial. A base, generally cesium carbonate (68 mg, 0.21 mmol, 1.40 eq) is added to each reaction vial, and the vials are capped and placed in a shaker oven and heated at 100°C for 48 hours. The reaction mixtures are then cooled, and the reaction solvents are removed by evaporation. The solid residue is suspended in 400 μL of ethyl acetate and filtered

15 to remove all catalyst. The filtrates are concentrated to dryness by evaporation to provide compounds of Formula I, wherein the benzoic acid portion is esterified (e.g., benzyl or methyl ester). The esters are dissolved in 500 μL of THF/ethanol (1:1 v/v) to which is added 300 μL of 5 M sodium hydroxide. The solutions are shaken for 5 hours at 60°C and then cooled and concentrated to dryness by

20 evaporation of the solvents to provide the desired compounds of Formula I. Typical compounds prepared by this method are as follows. The structure of the compounds are generally confirmed by mass spectral analysis.

EXAMPLE 83

2-(3',5'-Dichloro-3-methyl-biphenyl-4-ylamino)-benzoic acid

MS: 371; MW: 372.2495.

EXAMPLE 84

2-(3',5'-Dibromo-3-methyl-biphenyl-4-ylamino)-benzoic acid

MS: 459; MW: 461.1515.

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EXAMPLE 85

2-(4-1,3-Benzodioxol-5-yl-2-methyl-phenylamino)-benzoic acid

MS: 347; MW: 347.3683.

EXAMPLE 86

5 2-(2,2',4'-Trichloro-biphenyl-4-ylamino)-benzoic acid

MS: 391; MW: 392.6678.

EXAMPLE 87

2-(2-Chloro-3',4'-difluoro-biphenyl-4-ylamino)-benzoic acid

MS: 359; MW: 359.7578.

10

EXAMPLE 88

2-(3'-Bromo-2-chloro-biphenyl-4-ylamino)-benzoic acid

MS: 401; MW: 402.6737.

EXAMPLE 89

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid

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EXAMPLE 90

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid

EXAMPLE 91

3-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 92

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5-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid

EXAMPLE 93

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 94

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,5-dimethoxy-benzoic acid

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EXAMPLE 95

2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-3-nitro-benzoic acid

EXAMPLE 96

3-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 97

5-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-isophthalic acid

EXAMPLE 98

2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 99

4-(4-{2-[(4aS,8aR)-4-(Octahydro-isoquinolin-2-yl)-phenyl]-ethyl}-phenylamino)-benzoic acid

EXAMPLE 100

2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-5-methoxy-benzoic acid

EXAMPLE 101

2-{4-[2-(3-Methoxy-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 102

2-{4-[2-(3-Bromo-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 103

2-{4-[2-(3-Fluoro-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 104

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid

EXAMPLE 105

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-nicotinic acid

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EXAMPLE 106

2-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-2,3-dihydro-1H-isindol-5-ylamino]-benzoic acid

EXAMPLE 107

5 2-{4-[2-(3-Fluoro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid

EXAMPLE 108

2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-5-nitro-benzoic acid

EXAMPLE 109

4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-benzoic acid

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EXAMPLE 110

4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-methoxy-6-nitro-benzoic acid

EXAMPLE 111

4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-methoxy-benzoic acid

15

EXAMPLE 112

2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid

EXAMPLE 113

20

{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenyl}-(2-methoxy-5-nitro-phenyl)-amine

EXAMPLE 114

2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-nitro-benzoic acid

EXAMPLE 115

3-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-benzoic acid

25 2-{3-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 182-184°C.

2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid; mp 153-154°C.

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EXAMPLE 135

2-{4-[5-(3,4-Dichloro-phenyl)-pentyl]-phenylamino}-benzoic acid; mp 106-108°C.

EXAMPLE 136

5 2-{4-[2-(4-{2-Hydroxycarbonylphenylamino}phenyl)ethyl]-phenylamino}-benzoic acid; MS 451 (M⁻¹).

EXAMPLE 137

2-(3',5'-Dichloro-biphenyl-4-ylamino)-benzoic acid; mp >220°C.

EXAMPLE 138

10 4-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-2-methoxy-5-nitro-benzoic acid; mp 74-78°C.

EXAMPLE 139

2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-5-fluoro-benzoic acid; mp 122-123°C.

15

EXAMPLE 140

5-Amino-2-{4-[5-(3,4-dichloro-phenyl)-pentyl]-phenylamino}-benzoic acid; mp 182-184°C.

EXAMPLE 141

20

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-C,C,C-trifluoro-methanesulfonamide; MS 531 (M⁻).

EXAMPLE 142

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-benzenesulfonamide; MS 539.

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EXAMPLE 143

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid; mp 190-192°C. MS 453 (M^{-1}).

EXAMPLE 144

5 4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic acid; mp 264-266°C.

EXAMPLE 145

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-trifluoromethyl-benzoic acid; mp 134-136°C; MS 454 (M^{+}).

10

EXAMPLE 146

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid; MS 454 (M^{+}).

EXAMPLE 147

15

2-((4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl)-methyl-amino)-5-dimethylamino-benzoic acid; mp 128-131°C.

EXAMPLE 148

2-((4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl)-methyl-amino)-benzoic acid; MS 400 (M^{+}).

EXAMPLE 149

20

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-dipropylamino-benzoic acid; MS 485 (M^{+}).

EXAMPLE 150

5-Dibutylamino-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid; MS 513 (M^{+}).

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EXAMPLE 151

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-diethylamino-benzoic acid;
mp 106-110°C.

EXAMPLE 152

5 2,2'-[1,2-Ethanediy]bis (4,1-phenyleneimino)]bis-benzoic acid

EXAMPLE 153

4-[3-[4-(Diethylamino)phenyl]propyl]-N-(2-methoxy-5-nitrophenyl)-benzinamine

EXAMPLE 154

2-{3-[2-(4-Chlorophenyl)ethyl]phenylamino}-benzoic acid

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EXAMPLE 155

2-{3-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-benzoic acid

EXAMPLE 156

2-{3-[3-(4-Diethylaminophenyl)propyl]phenylamino}-benzoic acid

EXAMPLE 157

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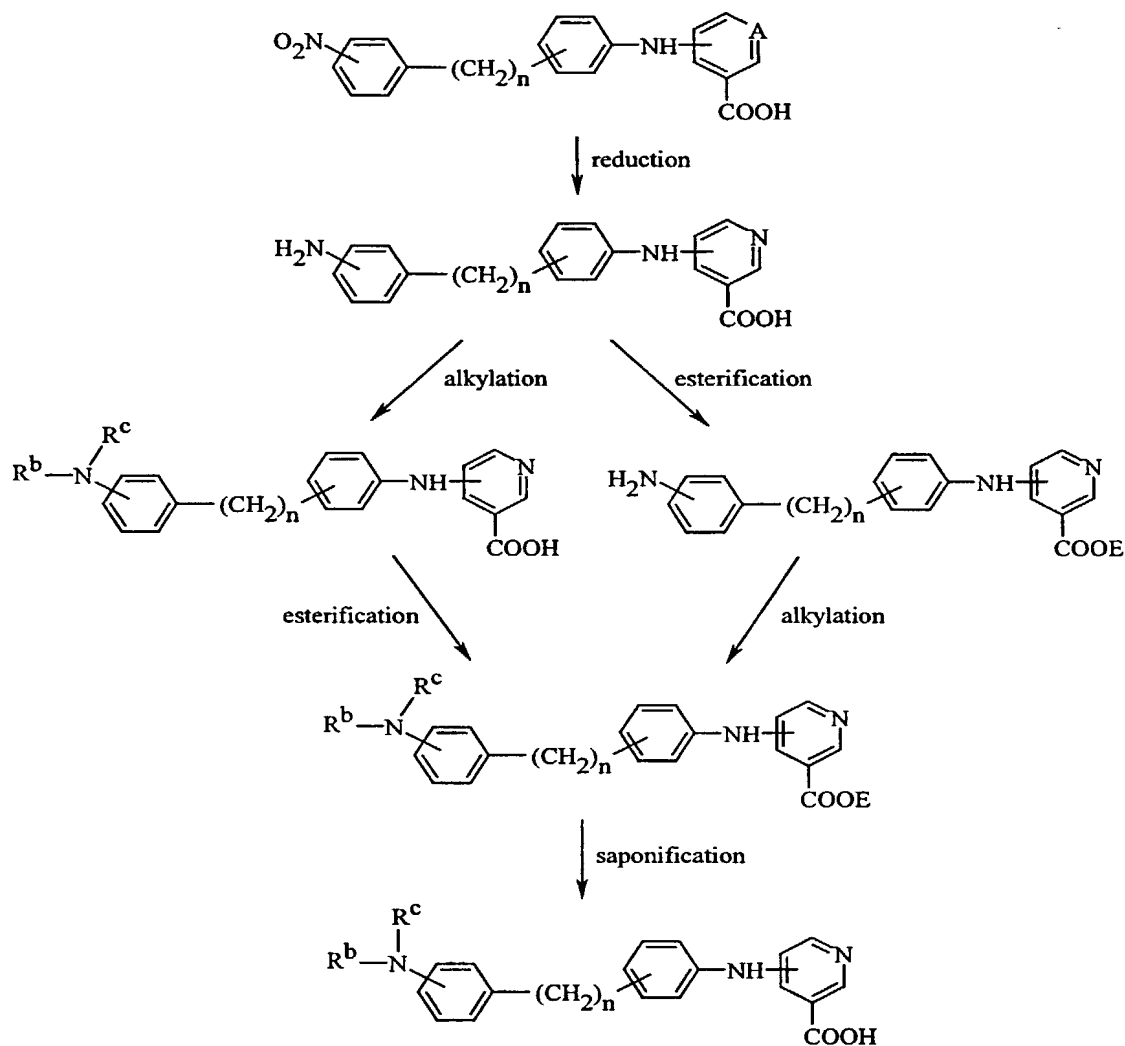
2-{3-[3-(4-Di-n-propylaminophenyl)propyl]phenylamino}-benzoic acid

20

The following Examples 158-163 illustrate the use of invention compounds as starting materials and intermediates in the synthesis of other invention compounds and derivatives. The examples illustrate reduction of nitro groups to amino groups, alkylation of amino group, and esterification of carboxylic acid groups. These reactions are depicted in the following generalized Scheme 12.

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Scheme 12



where R^b and R^c are as defined above, and E is an ester forming group such as C_1 - C_6 alkyl (e.g., methyl, 2,2,2-trichloroethyl), benzyl, diphenylmethyl, or the like.

EXAMPLE 158

2-{4-[3-(4-Nitrophenyl)propyl]phenylamino}benzoic acid

To a slurry of 4-[3-(4-nitrophenyl)propyl]aniline (4.08 g, 15.9 mmol) and 2-bromobenzoic acid (3.52 g, 17.5 mmol) in i-PrOH (100 mL) was added

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Cu(OAc)₂ (87 mg, 0.478 mmol) and KOAc (3.44 g, 35.0 mmol) at room temperature. The resulting mixture was allowed to heat under reflux for 23 hours, then cooled to room temperature. After removing the solvent under reduced pressure, the residue was diluted with water (100 mL) and basified with aqueous 1.0 M-NaOH solution to pH 9.0. The aqueous layer was washed with Et₂O (20 mL, twice) and acidified with aqueous 1.0 M-HCl solution to pH 3.0. The precipitate formed was filtered by suction and dried at 60°C in vacuo, affording the title compound as a beige solid (5.75 g, 96% yield). mp 150-153°C. MS (Fab): 376 (MH⁺).

EXAMPLE 159

2-{4-[3-(4-Aminophenyl)propyl]phenylamino}benzoic acid

To a solution of 2-{4-[3-(4-nitrophenyl)propyl]phenylamino}benzoic acid (Example 158) (3.0 g, 7.97 mmol) in DMF (40 mL) was added 10% Pd-C (300 mg) at room temperature under argon atmosphere. Hydrogen gas (1 atm) was introduced into the flask and the mixture was stirred for 14 hours at room temperature. The reaction mixture was filtered through a Celite pad to remove Pd-C and concentrated in vacuo. The residue was diluted with MeOH (ca. 50 mL) and concentrated in vacuo. This operation was repeated 3 times to remove any trace of DMF. The residue was diluted with MeOH again, and insoluble stuff was removed by filtration. Removing the solvent of the filtrate in vacuo afforded an oil, which was diluted with CH₃CN (50 mL) and added dropwise water (100 mL) slowly. The precipitate formed was filtered and dried at 60°C in vacuo, affording the title compound as a white solid (2.34 g, 85% yield). mp 110-112°C. MS (Fab): 347 (MH⁺).

EXAMPLE 160

2-{4-[3-(4-Aminophenyl)propyl]phenylamino}benzoic acid methyl ester

To a solution of 2-{4-[3-(4-aminophenyl)propyl]phenylamino}benzoic acid (Example 159) (2.34 g, 6.75 mmol) in MeOH (50 mL) was added concentrated H₂SO₄ (1.0 mL) at room temperature. The mixture was stirred under reflux for 3.0 days. The reaction was quenched with Et₃N (10 mL) at 5°C, and the

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solvent was removed under reduced pressure. The residue was diluted with water (20 mL) and extracted with Et₂O (20 mL, 4 times). The combined ether layer was washed with water (10 mL) and brine (10 mL), and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and purification by column chromatography afforded crude title compound as a yellow amorphous material (2.59 g). This material was used without further purification.

EXAMPLE 161

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid methyl ester and 2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino}benzoic acid methyl ester

To a solution of the crude ester described above (2.59 g, ca. 6.75 mmol) and CH₃CHO (2.0 mL, 35.1 mmol) in CH₃CN (50 mL) was added NaBH₃CN (1.70 g, 27.0 mmol) at 5°C, and the suspension was stirred for 30 minutes while the pH was monitored and aqueous 1.0 M-HCl solution was added to maintain the mixture moderately acidic (pH 3.0-4.0). The reaction mixture was allowed to warm up to room temperature over 1.0 hour and then basified with aqueous 1.0 M-NaOH solution to pH 9.0. The reaction mixture was concentrated under reduced pressure to remove CH₃CN, and the resulting aqueous solution was acidified with aqueous 1.0 M-HCl solution to pH 3.0. The aqueous solution was extracted with CHCl₃ (20 mL, 3 times), and the combined extract was washed with brine (5 mL). After drying over anhydrous Na₂SO₄, the solvent was removed under reduced pressure and purified by column chromatography (silica gel 60N, n-hexane/CHCl₃/Et₃N 50:98:2). First eluted was the dialkylated product as a yellow amorphous material (1.07 g, 38%).

MS (Fab): 417 (MH⁺).

Subsequently eluted was the monoalkylated product as a yellow amorphous material (0.79 g, 30%).

MS (Fab): 389 (MH⁺).

EXAMPLE 162

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid

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To an emulsion of 2-{4-[3-(4-diethylaminophenyl)propyl]phenylamino}-benzoic acid methyl ester (1.68 g, 4.03 mmol) in EtOH (50 mL) was added aqueous 3 M-KOH solution (4.0 mL, 12.0 mmol) at room temperature, then the mixture was allowed to heat under reflux for 40 minutes. The reaction mixture was cooled to room temperature and neutralized with aqueous 1.0 M-HCl solution to pH 9.0. The mixture was concentrated under reduced pressure to remove EtOH, and the resulting aqueous solution was extracted with CHCl₃ (50 mL, 3 times). The combined extract was washed with brine (10 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and purification by column chromatography (silica gel 60N, conc NH₄OH/MeOH/CHCl₃ 0.2:2:100 to 0.5:5:100) afforded a yellow oil. This oil was diluted with acetone, and the solution was concentrated under reduced pressure at room temperature to give the title compound as an amorphous solid (1.62 g, 99% for 0.2 hydrate).

MS (Fab): 403 (MH⁺).

Analysis for C₂₆H₃₀N₂O₂·0.20 H₂O: Calcd: C, 76.89; H, 7.54; N, 6.90.

Found: C, 76.73; H, 7.67; N, 7.10.

EXAMPLE 163

2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino}benzoic acid

The title compound was prepared from 2-{4-[3-(4-ethylaminophenyl)propyl]phenylamino}benzoic acid methyl ester (from Example 161), EtOH (10 mL), and 3 M-KOH solution (1.0 mL) using the procedure described in Example 162. This procedure yielded a yellow solid, 253 mg of the desired product (90% for 0.1 hydrate).

MS (Fab): 375 (MH⁺).

Analysis for C₂₄H₂₆N₂O₂·0.10 H₂O: Calcd: C, 76.61; H, 7.02; N, 7.44.

Found: C, 76.62; H, 7.06; N, 7.36.

BIOLOGICAL EXAMPLES

Representative compounds of Formula I have been evaluated in several in vitro and in vivo assays which are well-established as indicative of clinical usefulness in treating Alzheimer's disease.

5 AMYLOID ASSAYS**BASSR (Beta-Amyloid Self-Seeding Radioassay)**

An assay for inhibitors of self-seeded amyloid fibril growth

Materials:**Stock Solutions:**

10 *Assay Buffer* - 50 mM sodium phosphate, pH 7.5, 100 mM NaCl, 0.02% NaN₃,
1 M urea (filter and store at 4°C).

Soluble A β (1-40) peptide (Bachem, Torrance, CA) - 2.2 mg/mL in deionized H₂O
(stored in aliquots at -20°C, keep on ice when thawed) will self-seed after 1 week
storage. Typically, the solution should be stored until no lag phase is seen in the
15 assay.

¹²⁵I-labeled A β (1-40) - 150K-350K cpm/ μ L in 100% acetonitrile - 0.1%
trifluoroacetic acid (TFA) - 1% β -mercaptoethanol (aliquots stored at -20°C).

¹²⁵I-labeled A β (1-40) can be made in accordance with the procedure set forth by
H. LeVine, III in *Neurobiol. Aging*, **16**, 755, (1995), which is hereby incorporated
20 by reference, or this reagent may be purchased from Amersham, Arlington
Heights, Illinois.

Final assay conditions: 30 μ M soluble A β (1-40) in deionized water in assay
buffer + 20K-50K cpm ¹²⁵I-labeled A β (1-40) per assay. Compound to be tested
is dissolved in dimethylsulfoxide (DMSO), typically 5 to 50 mM stock, such that
25 the final concentration of DMSO is <1% v/v in the assay.

30 Stock Solutions:

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Assay Buffer - 50 mM sodium phosphate, pH 7.5, 100 mM NaCl, 0.02% NaN₃,
1 M urea (filter and store at 4°C)

Soluble Aβ (1-40) - 2.2 mg/mL in deionized H₂O (store in aliquots at -20°C, keep
on ice when thawed) will self-seed after 1 week storage. Typically, the solution
should be stored until no lag phase is seen in the assay.

Final assay conditions: 30 μM soluble Aβ (1-40) in deionized water in assay
buffer. Compound to be tested is dissolved in DMSO, typically 5 to 50 mM stock,
such that the final concentration of DMSO is <1% v/v in the assay.

Assay: Reaction mixture for 50 assays (on ice) comprised of 1 μL of soluble
Aβ (1-40) + 13.5 μL assay buffer per assay. The following are the amounts of the
components of the reaction mixture that result in each of the 50 assay wells:

50 μL soluble Aβ (1-40)

675 μL assay buffer

Assay Method

- 1) Prepare the reaction mix above by mixing the components and storing on ice.
- 2) Pipet 14.5 μL of reaction mixture into each of 50 wells of a polystyrene U-bottom 96-well microtiter plate (Corning 25881-96) on ice.
- 3) Add 1.7 μL of diluted compound to be tested to each well in a column of eight, including solvent control. Serial 3-fold dilutions from 1 mM (100 μM final) in assay buffer - urea = 7 dilutions + zero. Each 96-well plate can therefore accommodate 11 samples + 1 Congo Red control (0.039-5 μM final in 2-fold steps).
- 4) Seal the plate with aluminum film and incubate for 10 minutes on ice.
- 5) Raise the temperature to 37°C and incubate for 3 to 5 hours (depends on the lot of the peptide).
- 6) Remove the aluminum film and add 250 μL/well of 5 μM thioflavin T (ThT) [T-3516, Sigma-Aldrich] in 50 mM glycine-NaOH, pH 8.5. Read

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fluorescence on a plate reader (ex = 440 nm/20 nm ; em = 485 nm/20 nm)
within 5 minutes.

BAPA (Beta-Amyloid Peptide Aggregation)

This assay is used to provide a measure of inhibition by a compound
5 against the aggregation behavior of the beta amyloid peptide.

The purpose of this assays is to provide a higher volume method of
assaying the amount of beta amyloid aggregation using an endpoint assay based
on filtration. In this assay, hexafluoroisopropanol (HFIP) is used to break down
the initial amyloid peptide to a monomer state and use a concentration of 33 μ M
10 which is high enough so that aggregation will occur at pH 6.0 in several hours.

METHODS:

β -Amyloid Peptide Aggregation, pH 6.0 (BAPA)

In a 96-well plate (Costar 3794), we add 25 μ L 50 mM Phosphate Buffer,
pH 6.0, 10 μ L 0.5 mg/mL A β (1-40) peptide in 20% HFIP + 0.1 μ L/assay
15 radioiodinated 125 I A β (1-40) [125 I A β (1-40)], and 1 μ L of the compound to be
tested starting at 50 mM with a concentration of DMSO <1%. Then, we incubate
for 2 to 4 hours at room temperature. We stop the reaction with 200 μ L of 50 mM
phosphate buffer, pH 6.0, and filter it through a 0.2 μ m 96-well filter plate
(Millipore MAGU N22). We wash the filter plate with 100 μ L of the same
20 phosphate buffer. Aggregation was detected on a Microbeta counter after
impregnating the filters with Meltilex (1450-441) and is corrected for background.

BATYM ASSAY

METHODS:

Required A β (1-42) (California Peptide) was dried from its
25 hexafluoroisopropanol (HFIP) stock solution. The A β (1-42) was dissolved in
dimethylsulfoxide (DMSO) and then mixed with phosphate buffered saline (PBS)
(pH 7.4). The mixed A β (1-42) solution was filtered with a 0.2 μ m Omnipore
membrane syringe filter (Millipore, Bedford, MA). The compound to be tested in
DMSO (50 times concentrate) was put into each well (0.5 μ L/well) of a 96-well

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plate. The A β (1-42) solution was added into each well (24.5 μ L/well). The plate was centrifuged at 1,000 g for 5 minutes and incubated at 37°C for 1 day (A β 1-42; final concentration 100 μ M).

After incubation Thioflavin T (ThT) (30 μ M) solution in glycine-NaOH buffer (pH 8.5, 50 mM) was added into each well (250 μ L/well), fluorescence was measured (ex = 440/20 nm, em = 485/20 nm) using a fluorescence plate reader. The inhibitory activity was calculated as the reduction of fluorescence with the following formula:

$$\text{Inhibition (\%)} = \{F(A\beta) - F(A\beta + \text{compound})\} / \{F(A\beta) - F(\text{solvent} + \text{compound})\} \times 100$$

The IC₅₀s were calculated by a curve fitting program using the following equation. The data were obtained from two different experiments in triplicate.

$$\text{Inhibition}(x) = 100 - 100 / \{1 + (x/IC_{50})^n\},$$

x = Concentration of tested compound (M),

IC₅₀ = (M),

n = Hill coefficient.

Representative compounds of Formula I have exhibited inhibitory activities (IC₅₀) ranging from 0.1 μ M to greater than 100 μ M in the foregoing assays.

The results of these assays for specific and representative compounds of the present invention are shown in Table 1 below.

Table 1. β -Amyloid Inhibitory Activity of Compounds of Formula I

Example No.	BASSR (IC ₅₀ = μ M)	BASST (IC ₅₀ = μ M)	BATYM (IC ₅₀ = μ M)	BAPA (IC ₅₀ = μ M)
1	10 (P), >100 (P) (6 \times), >100 (Q), >100 (R), >100 (S), 52 (T) >100 (Z)	2, 4, 30, 10 (P) 3(Q) >100 (R) 11 (S), 11 (T) 6(Z)	50, 58.8 (P) 57.8 (Q)	60 (P), >100 (P) 86 (Q), >60 (R), >60 (S), 11 (T)
2	2.2, 4.1, 4.1, 12, 4.5	1, 1.5 (P)	6.52 (P)	70 (P)
3	4.5, 5, 5 (all 3 V-shaped) (P) 15 (ppt), 5 (Q)	2 (P) 3 (Q)	11.7 (P)	>60 (P)
4	30, >100 (3 \times)	3, 4, 8	26.3, 30.7	67
5	70, >100	4.5	10	74
6	15, 21, 20, 40	4, 1, 3	21.5	>60
7	18, 13, 12, 20	2	8.83	39
8	15, 15, 18, 15	3, >100	7.17	
9	20 (ppt), 30, 52, 40 (P)	1, 2 (P)	20.1, 28.2 (P) 38.6 (R)	75 (P)
10	70, 50	4	75.7	67
11	18 (ppt), 20 (ppt), 20 (2 \times), >100 (P) >100, 21, 30 (Q)	1, 1, 3 (P) 1, 0.8 (Q)	5.62 (P) 6.78 (Q)	23 (P) 9 (Q)
12	20 (4 \times)	1, 1	3.93	>60
13	21, >100, 20 (ppt), 15 (ppt), >100	0.9	6.41	6
14	18 (ppt), 8, 6 (ppt), 7 (ppt)	1.0	10.9	>10 (V-shaped)
15	100 (3 \times) P 100, 16 (V-shaped) 12, 15, 11 (Q)	1 (P) 1.2 (Q)	8.52 (P) 7.26 (Q) 7.07 (Q)	>60 (P) 7 (Q)

Example No.	BASSR (IC ₅₀ = μM)	BASST (IC ₅₀ = μM)	BATYM (IC ₅₀ = μM)	BAPA (IC ₅₀ = μM)
16	18, 7.5, 10 (P) 70, 32, 42 (Q)	3, 0, 3 (P) 1.1, 0.8, 0.6 (Q)	12 (P) 10.3 (Q)	13 (P)
17	>100 (ppt) (3×)	6.2	64.5	>60 (Q), 41 (R)
18	>100 (5×) (P)	30, >100 (P)	>100 (P)	9, >40, 53 (P), 12
19	3, 4, >100, 2.2	>100, 1, 1, 1.5	31.0, 34.0	>60, 43
20	4.2	6	68.6	22
21	3	4	62.7	26
22	3	9	>100	24
23	20	2	>100	17
24	>100	20	>100	91
25	>100	4	21.1	47
26	>100	1	>100	57
27	>100	3	19.8	74
28	>100	5	42.3	27
29	>100	4	38.1	30
30	30, 20	4, 2	75.3	38
31	>100	1	22.6	86
32	>100	1	29.2	96
33	>100	>100	>100	>10
34	45	3	45.0	48
35	>100	100	>100	154
36	>100	>100	>100	149
37	>100	0.8	30.2	25
38	20, 10 (V)	3	23.4	184
39	>100	20	>100	21
40	>100	3.0	>100	53
41	>100	5	49.7	42
42	>100	2	55.6	30
43	>100	0.3	24.2	63
44	>100	1	26.5	52
45	>100	1	21.5	32
46	>100	6	34.3	
47	>100	2	38.2	
48	25	10	>100	
49	>100	>100	>100	
50	>100	>100	>100	
51	85	0.8	39.1	

Example No.	BASSR (IC ₅₀ = μM)	BASST (IC ₅₀ = μM)	BATYM (IC ₅₀ = μM)	BAPA (IC ₅₀ = μM)
52	75	0.5	36.5	
53	>100	0.3	30.0	
54	>100	0.4	43.9	
55	12	2	5.1	101
56	>100	3	11.5	30
57	4.8	1.5	4.0	50
58	3.5	1	5.1	60
59	>100	>100	>100	3
60	>100	3	40.7	8
61	18, 7.5, 10	3, 0.3	12	13
62	>100	1.5	8.98	
63	15, 15, 18 (ppt)	1	9.43	45
64	>100	5	35	>100
65	60, 80	1.5	15.9	>100 (V-shaped)
66	>100 (ppt), >100 (ppt)	2.1	50.1	>100
67	41	4	13.3	>60
68	>100, >100	1	>100	110
69	2 (V-shaped), 3.5 (ppt)	0.8	11.7	58
70	20, 100	10	>100	65
71	>100	3		>60
72	40, 15, 12	2, 2.5	74.8	>60, >60
73	25, 35, 40	0.3	9.43	>60
74	6, 18, 19, 18	0.3, 0.5	8.36	>60
75	>100	2.2	46.2	>60
76	3	0.5	8.59	>60
77	18, 15	8, 0.3	9.49	>60
78	70	0.1	>100	8
79	3.1, 50, 38, 70, 70, 30, 40	1, 0.3, 0.3, 0.3	9.14	51
80	>100	4	24.8	>60
81	>100	15	48.4	73
82	>100, >100, >100	2, 0.3, 0.3		
83	>100	>100		9, 47, 29
84	>100	>100		5, 40, 21
85	>100	18		8, 77, 45

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Table 1. β -Amyloid Inhibitory Activity of Compounds of Formula I (cont'd)

Example No.	BASSR (IC ₅₀ = μ M)	BASST (IC ₅₀ = μ M)	BATYM (IC ₅₀ = μ M)	BAPA (IC ₅₀ = μ M)
86	40	18		>10, 89, 37
87	>100	50		>10, 15, 32
88	>100	10		>10, 37, 27
116	>100, >100	18, 30		96
117	>100	3	61.3	>100
118	>100, >100	6		>60
119	>100	3		>60
120	>100	3		>60
121	>100, >100	1		
122	>100	2	>100	>60
123	>100 (3 \times), 14 4, 18, >100, >100 (Q)	3, 3 3.2, 4 (Q)	70.8 85.2 (Q)	>60 (Q)
124	>100	10	62.7	
125	82	10	>100	80
126	>100, >100 30, 100 (Q)	4, 5 10, 4 (Q)	84 73.9 (Q)	63 >60 (Q)
127	>100 (ppt)	10	>100	67
128	>100 (ppt) (4 \times) 11, >100 (3 \times) 15, 20, 10, 7.5 (Q) 15, >100 (3 \times) Q	10, 41, 6 7, 3, 3 (Q)	75 >60 (Q)	60 >60 (Q)
129	1 (V-shaped) (2 \times) >100 (ppt)	10, 3, 2, 2	>100	>102
130	>100 (3 \times)	2, >100, 50	47.5	238
131	>100	10	93.5	>60
132	>100	10	>100	60
133	>100	>100	>100	>60
134	>100	2	36.5	>60
135	>100	1.2	31.2	>60
136	>100	3	>100	53
137	>100, >100	3		52
141	>100	7	56.7	>50
142	>100	2.1	26.9	55
143	>100 (4 \times)	40, 30	>100	2, >60, >60
144	15, 25	40	>100	114

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Table 1. β -Amyloid Inhibitory Activity of Compounds of Formula I (cont'd)

Example No.	BASSR (IC ₅₀ = μ M)	BASST (IC ₅₀ = μ M)	BATYM (IC ₅₀ = μ M)	BAPA (IC ₅₀ = μ M)
145	10, 40, 30	4	56.8	9
146	>100	30	>100	>60
147	>100	10	93.4	>60
148	>100		>100	
149	>100	>100	>100	>60
150	>100	10	>100	76
151	>100, >100	5, >100	>100	108
154	>100	3, 30	70.8	
155	>100	3	44.6	
156			27.8	
157			25.9	

A letter in parentheses after particular value indicates the particular synthetic lot of the compound tested. The terms "P," "Q," "R," "S," "T," and "Z" designate different lots of the same compound. For example, 10 (P) indicates that compound tested was from Lot P. If no lot is specified, the lot of the compound was Lot P.

The abbreviation "ppt" means precipitate and indicates that a precipitate formed at the indicated concentration. In addition, the term "V-shaped" means that inhibition was observed followed by precipitation.

A value followed by a number and \times (i.e., 4 \times) means that the compound was tested four times, and each time the result was the same.

The invention compounds have also shown good activity in standard in vivo assays commonly used to evaluate agents to treat diseases related to aggregation of amyloid proteins, especially Alzheimer's disease and other amyloidoses. In one assay, amyloid protein is induced into the spleen of mice by subcutaneous injections of silver nitrate, Freund's complete adjuvant, and an intravenous injection of amyloid enhancing factor. Silver nitrate is administered each day through Day 11. Test compounds are administered to the mice daily starting on Day 1 through Day 11. On Day 12, the animals are sacrificed, and the spleens are removed, histologically prepared, stained with Congo red, and the percent area of the spleen occupied by birefringent, Congo red-stained amyloid is

The above data establishes that representative invention compounds are active in standard assays used to measure inhibition of protein aggregation. The compounds exhibit excellent specificity, for example, as shown in the BASST assay, as well as the BATYM and BAPA assays. The compounds are thus useful to clinically inhibit amyloid protein aggregation and to image amyloid deposits for diagnostic use. The compounds will be used in the form of pharmaceutical formulations, and the following examples illustrate typical compositions.

EXAMPLE 164

Tablet Formulation

Ingredient	Amount
Compound of Example 1	50 mg
Lactose	80 mg
Cornstarch (for mix)	10 mg
Cornstarch (for paste)	8 mg
Magnesium Stearate (1%)	2 mg
	150 mg

The compound of Example 1 is mixed with the lactose and cornstarch (for mix) and blended to uniformity to a powder. The cornstarch (for paste) is suspended in 6 mL of water and heated with stirring to form a paste. The paste is added to the mixed powder, and the mixture is granulated. The wet granules are passed through a No. 8 hard screen and dried at 50°C. The mixture is lubricated with 1% magnesium stearate and compressed into a tablet. The tablets are administered to a patient at the rate of 1 to 4 each day for prevention of amyloid protein aggregation and treatment of Alzheimer's disease.

EXAMPLE 165

Parenteral Solution

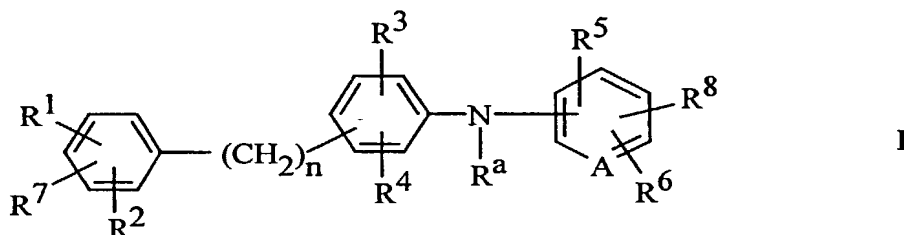
In a solution of 700 mL of propylene glycol and 200 mL of water for injection is added 20.0 g of Compound No. 19 (Example 19). The mixture is stirred and the pH is adjusted to 5.5 with hydrochloric acid. The volume is adjusted to 1000 mL with water for injection. The solution is sterilized, filled into 5.0 mL ampoules, each containing 2.0 mL (40 mg of Compound No. 19), and sealed under nitrogen. The solution is administered by injection to a patient suffering from medullary carcinoma of the thyroid and in need of treatment.

The invention and the manner and process of making and using it, are now described in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

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CLAIMS

What is claimed is:

1. A method of treating Alzheimer's disease, the method comprising administering to a patient having Alzheimer's disease a therapeutically effective amount of a compound of Formula I



wherein

O
||

R^a is hydrogen, C_1 - C_6 alkyl, or $-CC_1$ - C_6 alkyl;

n is 0 to 5 inclusive;

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 are independently hydrogen, halogen, $-OH$, $-NH_2$, NR^{bR^c} , $-CO_2H$, $-CO_2C_1$ - C_6 alkyl, $-NO_2$, $-OC_1$ - C_{12} alkyl, $-C_1$ - C_8 alkyl, $-CF_3$, $-CN$, $-OCH_2$ phenyl, $-OCH_2$ -substituted phenyl, $-(CH_2)_m$ -phenyl, $-O$ -phenyl, $-O$ -substituted phenyl,

O O
|| ||

$-CH=CH$ -phenyl, $-O(CH_2)_pNR^{bR^c}$, $-CNR^{bR^c}$, $-NHCR^b$,
 $-NH(CH_2)_pNR^{bR^c}$, $-N(C_1-C_6\text{alkyl})(CH_2)_pNR^{bR^c}$,

$$\begin{array}{c} \text{CH}_2\text{OC}_1\text{-C}_6\text{ alkyl} \\ \diagup \\ \text{---CH} \\ \diagdown \\ \text{CH}_2\text{OC}_1\text{-C}_6\text{ alkyl} \end{array};$$

R^8 is $COOH$, tetrazolyl, $-SO_2R^d$, or $-CONHSO_2R^d$;

R^b and R^c are independently hydrogen, $-C_1$ - C_6 alkyl, $-(CH_2)_m$ -phenyl, or

R^b and R^c taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidiny, pyrrolyl,

-OCH₂- substituted phenyl, pyrrolyl, or -N(phenyl)₂.

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5. The method of Claim 1 wherein

R^a is hydrogen;

n is 3, 4, or 5;

R^3 and R^4 are hydrogen; and

R^1 , R^2 , and R^7 are independently chlorine or hydrogen.

6. The method of Claim 1 wherein

R^a is hydrogen;

n is 2;

R^3 and R^4 are hydrogen; and

R^5 , R^6 , and R^8 are independently hydrogen, $-\text{CO}_2\text{H}$, $-\text{NO}_2$, $-\text{OCH}_3$,
imidazolyl, $-\text{CN}$, fluorine, $-\text{CH}_3$, $-\text{CF}_3$, halogen,
 $-\text{NH}-\text{C}_1-\text{C}_6$ alkyl, $-\text{N}(\text{C}_1-\text{C}_6\text{alkyl})_2$, $-\text{NH}_2$, or pyrrolyl.

7. The method of Claim 1 wherein

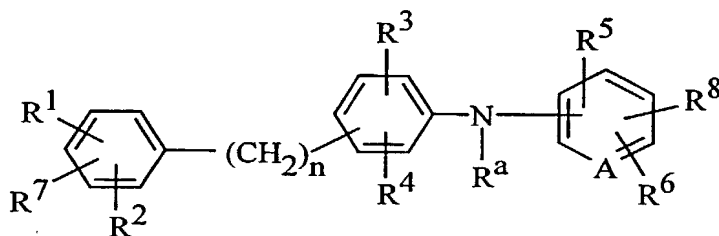
R^a is hydrogen;

n is 2;

R^3 and R^4 are hydrogen; and

R^5 is $-\text{CO}_2\text{H}$.

8. A method of treating Alzheimer's disease, the method comprising
administering to a patient having Alzheimer's disease a therapeutically
effective amount of a compound of Formula I



wherein

R^a is hydrogen;

n is 1 to 5 inclusive;

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R³ and R⁴ are hydrogen;

R¹, R⁷, and R² are independently chlorine, -N(CH₂CH₃)₂, -OH, CH₃-,
fluorine, -CF₃, phenyl, hydrogen, -OCH₂ phenyl,
-O(CH₂)₃N(CH₃)₂, -O phenyl, -O(CH₂)₇CH₃,
-CH(CH₂OCH₂CH₃)₂, pyrrolyl, -CH=CH-phenyl,
-N[(CH₂)₃CH₃]₂, substituted phenyl, -OCH₂-substituted phenyl,
pyrazolyl, or -N(phenyl)₂;

R⁵ and R⁶ are independently hydrogen, -CO₂H, -NO₂, -OCH₃,
imidazolyl, -CN, fluorine, -CH₃, -CF₃, or pyrrolyl;

R⁸ is COOH or tetrazolyl;
or the pharmaceutically acceptable salts thereof.

9. The method of Claim 1 wherein the compound of Formula I is:

2-[[4-[2-(3,4-Dichlorophenyl)ethyl]phenyl]amino]-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic
acid;

2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-
5-nitrobenzoic acid;

2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid;

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino}benzoic acid;

2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino}benzoic
acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-
5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-
1-yl-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino}benzoic acid;

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-
benzoic acid;

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- 2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-
3,5-dinitrobenzoic acid;
2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic
acid;
5 2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-
5-nitrobenzoic acid;
2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;
2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-
benzoic acid;
10 2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-
benzoic acid;
2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-
benzoic acid;
2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;
15 5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;
2-(4-Phenethyl-phenylamino)-benzoic acid;
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-
benzoic acid;
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic
20 acid;
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-
benzoic acid;
4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic
acid;
25 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-
methanesulfonyl-benzoic acid;
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-
yl-benzoic acid;
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-
30 benzoic acid;
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-
benzoic acid;

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2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-
benzoic acid;

5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-
benzoic acid;

5 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-
benzoic acid;

6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-
benzoic acid;

10 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-
benzoic acid;

15 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-
benzoic acid;

20 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-
trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-
trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-
trifluoromethyl-benzoic acid;

25 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-
benzoic acid;

2-{4-[2-(4-Benzyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-
phenylamino)-benzoic acid;

30 2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic
acid;

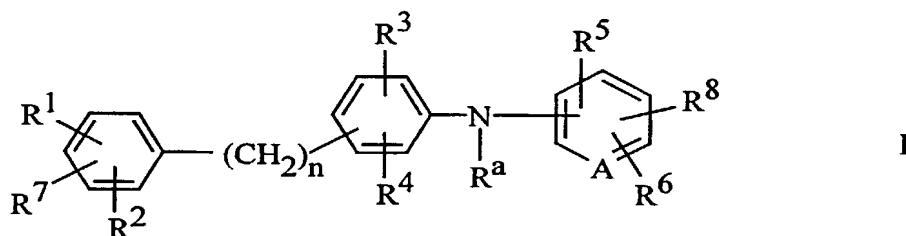
2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

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10. A method of inhibiting the aggregation of amyloid proteins to form amyloid deposits, the method comprising administering to a patient in need of inhibition of the aggregation of amyloid protein an amyloid protein aggregation inhibiting amount of a compound of Formula I



wherein

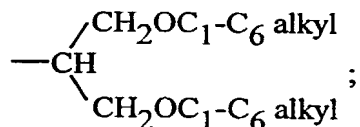


R^a is hydrogen, C_1 - C_6 alkyl, or $-CC_1$ - C_6 alkyl;

n is 0 to 5 inclusive;

R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 are independently hydrogen, halogen, $-OH$, $-NH_2$, NR^bR^c , $-CO_2H$, $-CO_2C_1$ - C_6 alkyl, $-NO_2$, $-OC_1$ - C_{12} alkyl, $-C_1$ - C_8 alkyl, $-CF_3$, $-CN$, $-OCH_2$ phenyl, $-OCH_2$ -substituted phenyl, $-(CH_2)_m$ -phenyl, $-O$ -phenyl, $-O$ -substituted phenyl,

15 $-CH=CH$ -phenyl, $-O(CH_2)_pNR^bR^c$, $-CNR^bR^c$, $-NHCR^b$, $-NH(CH_2)_pNR^bR^c$, $-N(C_1$ - C_6 alkyl) $(CH_2)_pNR^bR^c$,



20 R^8 is $COOH$, tetrazolyl, $-SO_2R^d$, or $-CONHSO_2R^d$;

R^b and R^c are independently hydrogen, $-C_1$ - C_6 alkyl, $-(CH_2)_m$ -phenyl, or

R^b and R^c taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl, imidazolyl, piperazinyl, 4- C_1 - C_6 alkylpiperazinyl, morpholino, 25 thiomorpholino, decahydroisoquinoline, or pyrazolyl;

25 14. The method of Claim 10 wherein

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R^a is hydrogen;

n is 3, 4, or 5;

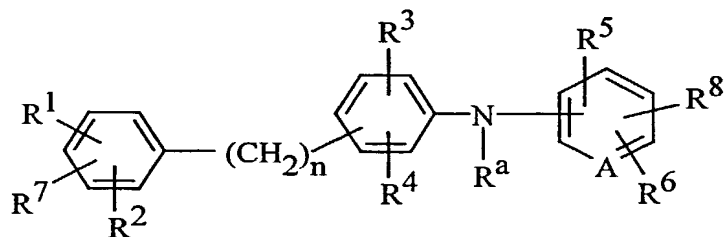
R^3 and R^4 are hydrogen; and

R^1 , R^2 , and R^7 are independently chlorine or hydrogen.

- 5 15. The method of Claim 10 wherein
 R^a is hydrogen;
 n is 2;
 R^3 and R^4 are hydrogen; and
 R^5 and R^6 are independently hydrogen, $-\text{CO}_2\text{H}$, $-\text{NO}_2$, $-\text{OCH}_3$,
 10 imidazolyl, $-\text{CN}$, fluorine, $-\text{CH}_3$, $-\text{CF}_3$, halogen,
 $-\text{NH}-\text{C}_1-\text{C}_6$ alkyl, $-\text{N}(\text{C}_1-\text{C}_6\text{alkyl})_2$, $-\text{NH}_2$, or pyrrolyl.

16. The method of Claim 10 wherein
 R^a is hydrogen;
 n is 2;
 15 R^3 and R^4 are hydrogen; and
 R^8 is $-\text{CO}_2\text{H}$.

17. A method of inhibiting the aggregation of amyloid proteins to form
 amyloid deposits, the method comprising administering to a patient in
 need of inhibition of the aggregation of amyloid protein an amyloid
 20 protein aggregation inhibiting amount of a compound of Formula I



I

wherein

R^a is hydrogen;

n is 1 to 5 inclusive;

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R³ and R⁴ are hydrogen;

R¹, R⁷, and R² are independently chlorine, -N(CH₂CH₃)₂, -OH, CH₃-,
fluorine, -CF₃, phenyl, hydrogen, -OCH₂ phenyl,
-O(CH₂)₃N(CH₃)₂, -O phenyl, -O(CH₂)₇CH₃,
5 -CH(CH₂OCH₂CH₃)₂, pyrrolyl, -CH=CH-phenyl,
-N[(CH₂)₃CH₃]₂, substituted phenyl, -OCH₂-substituted phenyl,
pyrazolyl, or -N(phenyl)₂;

R⁵ and R⁶ are independently hydrogen, -CO₂H, -NO₂, -OCH₃,
imidazolyl, -CN, fluorine, -CH₃, -CF₃, or pyrrolyl;

10 R⁸ is COOH or tetrazolyl;

A is CH or N;

R¹ and R², when adjacent to one another, can be methylene-dioxy;
or the pharmaceutically acceptable salts thereof.

18. The method of Claim 17 wherein the compound of Formula I is:

- 15 2-[[4-[2-(3,4-Dichlorophenyl)ethyl]phenyl]amino]-benzoic acid;
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic
acid;
2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-
5-nitrobenzoic acid;
20 2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino} benzoic acid;
2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino} benzoic acid;
2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino} benzoic
acid;
2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-
25 5-nitrobenzoic acid;
2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-
1-yl-5-nitrobenzoic acid;
2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino} benzoic acid;
2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino} benzoic acid;

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2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitro-
benzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-
3,5-dinitrobenzoic acid;

5 2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic
acid;

2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-
5-nitrobenzoic acid;

2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;

10 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitro-
benzoic acid;

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitro-
benzoic acid;

15 2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-
benzoic acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;

2-(4-Phenethyl-phenylamino)-benzoic acid;

20 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic
acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-
benzoic acid;

25 4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic
acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-
methanesulfonyl-benzoic acid;

30 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-
yl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-
benzoic acid;

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2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-
benzoic acid;

5 5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-
benzoic acid;

10 6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-
benzoic acid;

15 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-
benzoic acid;

20 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-
trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-
trifluoromethyl-benzoic acid;

25 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-
trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-
benzoic acid;

2-{4-[2-(4-Benzyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

30 2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-
phenylamino)-benzoic acid;

2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic
acid;

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2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-
 phenylamino)-benzoic acid;
 5 2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic
 acid;
 10 2-{4-[2-(4'-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic
 acid;
 2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-
 benzoic acid;
 15 2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-
 phenylamino)-benzoic acid;
 2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic
 acid;
 2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic
 acid;
 20 2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-
 phenylamino)-benzoic acid;
 2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic
 acid;
 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl] phenylamino}-5-
 25 nitrobenzoic acid;
 2-[[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-
 benzoic acid; or
 2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

19. The compounds:

30 2-{4-[4-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-4-methoxy-
 5-nitrobenzoic acid;
 2-{4-[2-(3,4-Dihydroxy-phenyl)-ethyl]-phenylamino}benzoic acid;

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2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]phenylamino} benzoic acid;

2-{4-[2-(3,4,5-Trihydroxy-phenyl)-ethyl]phenylamino} benzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}-4-imidazo-1-yl-5-nitrobenzoic acid; or

2-{4-[4-(3,4-Dichlorophenyl)butyl]phenylamino} benzoic acid.

20. The compounds:

2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-nitrobenzoic acid;

2-{4-[4-(3,4-Dichlorophenyl)-butyl]phenylamino}-3,5-dinitrobenzoic acid;

2-{4-[5-(3,4-Dichlorophenyl)pentyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[5-(3,4-Dichloro-phenyl)pentyl]phenylamino}-4-methoxy-5-nitrobenzoic acid;

2-[4-(3,4-Dichloro-benzyl)-phenylamino]-benzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-5-nitrobenzoic acid;

2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitrobenzoic acid;

2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid.

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid; or

2-{4-[2-(3,4-Dichlorophenyl)]phenylamino}-5-nitrobenzoic acid.

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21. The compounds:

2-(4-Phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-
benzoic acid;5 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-terephthalic
acid;2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methyl-
benzoic acid;10 4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic
acid;2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-
methanesulfonyl-benzoic acid;2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-imidazol-1-
yl-benzoic acid;15 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-nitro-
benzoic acid;2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-nitro-
benzoic acid; or20 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-nitro-
benzoic acid.

22. The compounds:

5-Cyano-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-
benzoic acid;25 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4,6-difluoro-
benzoic acid;6-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-2,3-difluoro-
benzoic acid;2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-fluoro-
benzoic acid;30 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-fluoro-
benzoic acid;

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2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-methyl-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-fluoro-
benzoic acid;

5 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3,5-difluoro-
benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-
trifluoromethyl-benzoic acid;

10 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-6-
trifluoromethyl-benzoic acid;

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(4-Nitrophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(3-Nitrophenyl)propyl]phenylamino} benzoic acid;

2-{4-[3-(4-Aminophenyl)propyl]phenylamino} benzoic acid;

15 2-{4-[3-(3-Aminophenyl)propyl]phenylamino} benzoic acid;

2-{4-[2-(4-Aminophenyl)phenylamino} benzoic acid;

2-{4-[2-(4-Dipropylaminophenyl)ethyl]phenylamino} benzoic acid
monohydrochloride;

20 2-{4-[2-(4-Diethylaminophenyl)ethyl]phenylamino} benzoic acid
monohydrochloride monohydrate;

2-{4-[3-(3-Dipropylaminophenyl)propyl]phenylamino} benzoic
acid;

2-{4-[3-(3-Dimethylaminophenyl)propyl]phenylamino} benzoic
acid;

25 2-{4-[3-(4-Ethylaminophenyl)propyl]phenylamino} benzoic acid;

2-(N-{4-[3-(4-Diethylaminophenyl)propyl]phenyl}-N-
ethylamino)benzoic acid;

2-{4-[2-(3-Dibenzylaminophenyl)ethyl]phenylamino} benzoic acid;

2-{4-[3-(3-Diethylaminophenyl)propyl]phenylamino} benzoic acid;

30 2-{4-[2-(3-Aminophenyl)ethyl]phenylamino} benzoic acid;

2-{4-[3-(4-Dimethylaminophenyl)propyl]phenylamino} benzoic
acid;

2-{4-[2-(4-Acetylaminophenyl)ethyl]phenylamino} benzoic acid;

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2-{4-[2-(3-Acetylaminophenyl)ethyl]phenylamino}benzoic acid;

2-{4-[2-(3-Dipropylaminophenyl)ethyl]phenylamino}benzoic acid
monohydrochloride;

2-{4-[2-(3-Dibutylaminophenyl)ethyl]phenylamino}benzoic acid
monohydrochloride;

2-{4-[3-(4-Acetylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Acetylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[2-(3-Diethylaminophenyl)ethyl]phenylamino}benzoic acid
monohydrochloride;

2-{4-[2-(3-Piperidin-1-ylphenyl)ethyl]phenylamino}benzoic acid
monohydrochloride;

2-{4-[3-(4-Dipropylaminophenyl)propyl]phenylamino}benzoic
acid;

2-{4-[3-(4-Dibutylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Dibutylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-(1H-Pyrrol-1-yl)phenyl)propyl]phenylamino}benzoic
acid;

2-{4-[3-(4-Piperidin-1-ylphenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Diethylcarbamoylphenyl)propyl]phenylamino}benzoic

acid;

2-{4-[3-(4-Carboxyphenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Diethylaminomethylphenyl)propyl]phenylamino}

benzoic acid;

2-{4-[3-(4-Propylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(3-Propylaminophenyl)propyl]phenylamino}benzoic acid;

2-{4-[3-(4-Pyrrolidin-1-yl-phenyl)-propyl]-phenylamino}-benzoic
acid;

2-{4-[3-(3-Piperidin-1-yl-phenyl)-propyl]-phenylamino}-benzoic
acid;

{5-[(1-Butyl-1,2,3,4-tetrahydro-6-quinolyl)methylidene]-4-oxo-2-
thioxothiazolidin-3-yl}acetic acid;

{5-[(1-Butyl-2,3-dihydro-1H-indol-5-yl)methylidene]-4-oxo-2-
thioxothiazolidin-3-yl}acetic acid;

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3-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}propanoic acid;

4-{5-[(1-Butyl-1,2,3,4-tetrahydroquinolin-6-yl)methylidene]-4-oxo-2-thioxo-thiazolidin-3-yl}butanoic acid;

5 2-{4-[3-(3,4-Dichloro-phenyl)-propyl]phenylamino}-5-methylbenzoic acid;

N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-methanesulofnamide;

10 2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-5-nitro-benzoic acid;

2-{4-[2-(4-Chloro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

15 5-Amino-2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

5-Nitro-2-(4-phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

20 2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-5-nitrobenzoic acid;

{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-[2-(1H-tetrazol-5-yl)-phenyl]-amine;

2-{4-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

25 2-(4-Phenethyl-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-fluoro-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-nicotinic acid;

30 2-{4-[2-(3-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

2-{4-[2-(4-Chloro-phenyl)-ethyl]-phenylamino}-5-nitro-benzoic acid;

30 2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-3-nitro-
benzoic acid;

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3-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

5-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-isophthalic acid;

5 2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

4-(4-{2-[(4aS,8aR)-4-(Octahydro-isoquinolin-2-yl)-phenyl]-ethyl}-phenylamino)-benzoic acid;

10 2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-5-methoxy-benzoic acid;

2-{4-[2-(3-Methoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3-Bromo-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(3-Fluoro-phenyl)-ethyl]-phenylamino}-benzoic acid;

15 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid;

4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-nicotinic acid;

2-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-2,3-dihydro-1H-isoindol-5-ylamino]-benzoic acid; or

20 2-{4-[2-(3-Fluoro-4-methyl-phenyl)-ethyl]-phenylamino}-benzoic acid.

23. The compounds:

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

25 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-pyrrol-1-yl-benzoic acid;

2-{4-[2-(4-Benzoyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3-Dimethylamino-propoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

30 2-{4-[2-(4-Diethylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyloxy-phenyl)-ethyl]-phenylamino}-benzoic acid;

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2-(4-{2-[4-(2-Ethoxy-1-ethoxymethyl-ethyl)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrrol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

or

2-{4-[2-(4-Styryl-phenyl)-ethyl]-phenylamino}-benzoic acid.

24. The compounds:

2-{4-[2-(4-Dibutylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4'-Ethyl-biphenyl-4-yl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Octyl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[3-(3,5-Dichloro-phenoxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-(4-{2-[4-(2-Chloro-6-fluoro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(4-Pyrazol-1-yl-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-{4-[2-(4-Diphenylamino-phenyl)-ethyl]-phenylamino}-benzoic acid;

2-(4-{2-[4-(3,4-Dichloro-benzyloxy)-phenyl]-ethyl}-phenylamino)-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichlorophenyl)]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-[(3,4-Dichlorophenyl)propyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[2-(3,4-Dimethyl-phenyl)-ethyl] phenylamino}-5-nitrobenzoic acid;

2-[4-(3,4-Dichlorophenyl)phenyl]aminobenzoic acid.

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25. 2-[4-[2-(3,4-Dichlorophenyl)ethyl]phenyl]amino-benzoic acid or a pharmaceutically acceptable salt thereof.
26. 2-{4-[3-(3,4-Dichlorophenyl)propyl]phenylamino}benzoic acid or a pharmaceutically acceptable salt thereof.
- 5 27. A compound which is selected from:
- 2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-5-nitro-benzoic acid;
- 4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-benzoic acid;
- 10 4-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-methoxy-benzoic acid;
- 2-{4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenylamino}-5-methoxy-benzoic acid;
- {4-[2-(3-Chloro-4-methyl-phenyl)-ethyl]-phenyl}-(2-methoxy-5-nitro-phenyl)-amine;
- 15 2-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-3-nitro-benzoic acid;
- 3-{4-[3-(4-Diethylamino-phenyl)-propyl]-phenylamino}-benzoic acid;
- 20 2-{4-[2-(3,4-Dimethoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid monosodium;
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid monopotassium;
- 25 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid calcium salt (1:1);
- 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoate-2-hydroxy-1,1-bis-hydroxymethyl-ethyl-ammonium;
- 30 2-{4-[4-(3,4-Dichloro-phenyl)-butyl]-phenylamino}-5-methoxy-benzoic acid;

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2-{4-[2-(3,4-Difluoro-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{3-[2-(4-Chloro-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{3-[2-(3,4-Dimethyl-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(2,4-Dimethoxy-phenyl)-ethyl]-phenylamino}-benzoic
 5 acid;
 2-{4-[2-(2-Chloro-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(2-Hydroxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(3-Chloro-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-[4-(2-Biphenyl-4-yl-ethyl)-phenylamino]-benzoic acid;
 10 2-{4-[2-(2,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;
 3-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;
 4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[2-(3,4,5-Trimethoxy-phenyl)-ethyl]-phenylamino}-benzoic
 acid;
 15 2-{4-[2-(4-Phenoxy-phenyl)-ethyl]-phenylamino}-benzoic acid;
 2-{4-[5-(3,4-Dichloro-phenyl)-pentyl]-phenylamino}-benzoic acid;
 2-(3',5'-Dichloro-biphenyl-4-ylamino)-benzoic acid;
 4-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-2-methoxy-
 5-nitro-benzoic acid;
 20 2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-5-fluoro-
 benzoic acid;
 5-Amino-2-{4-[5-(3,4-dichloro-phenyl)-pentyl]-phenylamino}-
 benzoic acid;
 N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-
 25 C,C,C-trifluoro-methanesulfonamide;
 N-(2-{4-[3-(3,4-Dichloro-phenyl)-propyl]-phenylamino}-benzoyl)-
 benzenesulfonamide;
 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-
 trifluoromethyl-benzoic acid;
 30 4-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-isophthalic
 acid;

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2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-4-trifluoromethyl-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-3-trifluoromethyl-benzoic acid;

5 2-({4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-methyl-amino)-5-dimethylamino-benzoic acid;

2-({4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenyl}-methyl-amino)-benzoic acid;

10 2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-dipropylamino-benzoic acid;

5-Dibutylamino-2-{4-[2-(3,4-dichloro-phenyl)-ethyl]-phenylamino}-benzoic acid;

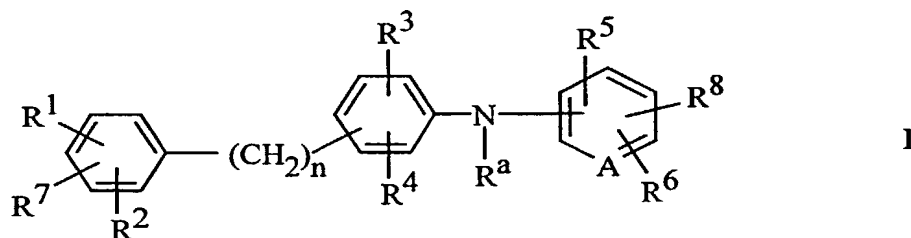
2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]-phenylamino}-5-diethylamino-benzoic acid;

15 2,2'-[1,2-Ethanediy]bis (4,1-phenyleneimino)]bis-benzoic acid; and

4-[3-[4-(Diethylamino)phenyl]propyl]-N-(2-methoxy-5-nitrophenyl)-benzinamine

28. A method of imaging amyloid deposits, the method comprising:

20 a. introducing into a patient a detectable quantity of a labeled compound having the Formula I or a pharmaceutically acceptable salt thereof:



wherein

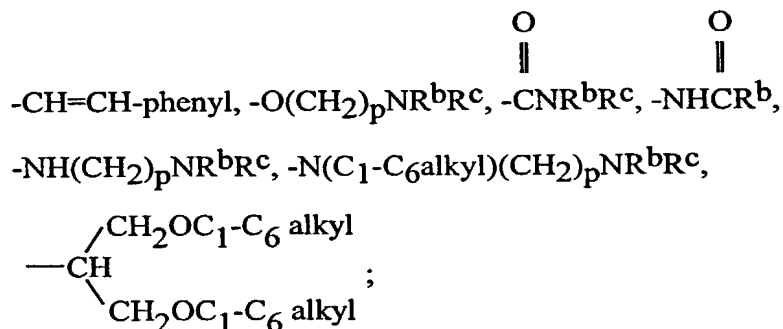
25

Ra is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, or -CC(=O)-C_6 alkyl;

n is 0 to 5 inclusive;

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$R^1, R^2, R^3, R^4, R^5, R^6$, and R^7 are independently hydrogen, halogen,
 -OH, -NH₂, NR^bR^c, -CO₂H, -CO₂C₁-C₆ alkyl, -NO₂, -OC₁-C₁₂
 alkyl, -C₁-C₈ alkyl, -CF₃, -CN, -OCH₂ phenyl, -OCH₂-substituted
 phenyl, -(CH₂)_m-phenyl, -O-phenyl, -O-substituted phenyl,



R^8 is COOH, tetrazolyl, -SO₂R^d, or -CONHSO₂R^d;

R^b and R^c are independently hydrogen, -C₁-C₆ alkyl, -(CH₂)_m-phenyl, or

R^b and R^c taken together with the nitrogen atom to which they are
 attached form a cyclic ring selected from piperidinyl, pyrrolyl,
 imidazolyl, piperazinyl, 4-C₁-C₆ alkylpiperazinyl, morpholino,
 thiomorpholino, decahydroisoquinoline, or pyrazolyl;

R^d is hydrogen, -C₁-C₆ alkyl, -CF₃, or phenyl;

m is 0 to 5 inclusive;

p is 1 to 5 inclusive;

A is CH or N;

R^1 and R^2 , when adjacent to one another, can be methylene-dioxy;
 or the pharmaceutically acceptable salts thereof.

b. allowing sufficient time for the labeled compound to become
 associated with amyloid deposits; and

c. detecting the labeled compound associated with the amyloid
 deposits.

29. The method of Claim 28 wherein the patient has or is suspected to have
 Alzheimer's disease.

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30. The method of Claim 28 wherein the labeled compound is a radio labeled compound.

31. The method of Claim 28 wherein the labeled compound is detected using MRI.

5 32. The compounds:

2-[4-[2-(3,4-Dichlorophenyl)ethyl]phenyl]amino-benzoic acid;

2-{4-[2-(3,4-Dichloro-phenyl)-ethyl]phenylamino}-5-nitrobenzoic acid;

2-{4-[3-(3,4-Dichlorophenyl)-propyl]phenylamino}benzoic acid;

10 2-[4-[2-(4-Chloro-3-trifluoromethylphenyl)ethyl]phenyl]amino-benzoic acid; and

2-{4-[3-(4-Diethylaminophenyl)propyl]phenylamino}benzoic acid.

15 33. A pharmaceutical formulation comprising a compound of Claim 19 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

34. A pharmaceutical formulation comprising a compound of Claim 20 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

20 35. A pharmaceutical formulation comprising a compound of Claim 21 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

36. A pharmaceutical formulation comprising a compound of Claim 22 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

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37. A pharmaceutical formulation comprising a compound of Claim 23 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

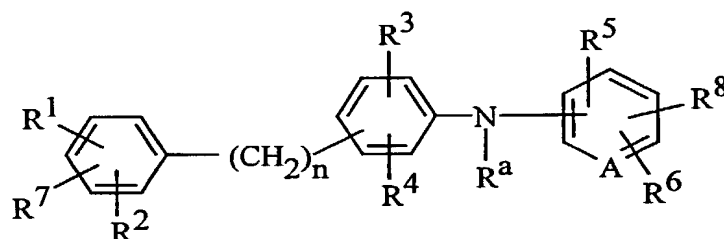
38. A pharmaceutical formulation comprising a compound of Claim 24 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

39. A pharmaceutical formulation comprising a compound of Claim 25 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

40. A pharmaceutical formulation comprising a compound of Claim 26 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

41. A pharmaceutical formulation comprising a compound of Claim 32 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

42. A compound of Formula I.



wherein



R^a is hydrogen, C_1 - C_6 alkyl, or $-CC_1$ - C_6 alkyl;

n is 0 to 5 inclusive;

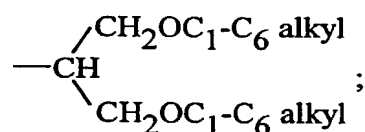
R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and R^7 are independently hydrogen, halogen,

$-OH$, $-NH_2$, NR^bR^c , $-CO_2H$, $-CO_2C_1$ - C_6 alkyl, $-NO_2$, $-OC_1$ - C_{12}

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alkyl, -C₁-C₈ alkyl, -CF₃, -CN, -OCH₂ phenyl, -OCH₂-substituted phenyl, -(CH₂)_m-phenyl, -O-phenyl, -O-substituted phenyl,

-CH=CH-phenyl, -O(CH₂)_pNR^bR^c, -C(=O)NR^bR^c, -NHCR^b,
 -NH(CH₂)_pNR^bR^c, -N(C₁-C₆alkyl)(CH₂)_pNR^bR^c,



R⁸ is COOH, tetrazolyl, -SO₂R^d, or -CONHSO₂R^d;

R^b and R^c are independently hydrogen, -C₁-C₆ alkyl, -(CH₂)_m-phenyl, or

R^b and R^c taken together with the nitrogen atom to which they are attached form a cyclic ring selected from piperidinyl, pyrrolyl, imidazolyl, piperazinyl, 4-C₁-C₆ alkylpiperazinyl, morpholino, thiomorpholino, decahydroisoquinoline, or pyrazolyl;

R^d is hydrogen, -C₁-C₆ alkyl, -CF₃, or phenyl;

m is 0 to 5 inclusive;

p is 1 to 5 inclusive;

A is CH or N;

R¹ and R², when adjacent to one another, can be methylene-dioxy; or the pharmaceutically acceptable salts thereof.

43. A pharmaceutical formulation comprising a compound of Claim 42 admixed with a pharmaceutically acceptable diluent, excipient, or carrier therefor.

NOTED

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

JAN 09 2001

(19) World Intellectual Property Organization
International Bureau

STRITENBERGER

(43) International Publication Date
21 December 2000 (21.12.2000)

PCT

(10) International Publication Number
WO 00/76489 A2(51) International Patent Classification⁷: A61K 31/00

(21) International Application Number: PCT/US00/15071

(22) International Filing Date: 31 May 2000 (31.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
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(81) Designated States (national): AE, AG, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA.

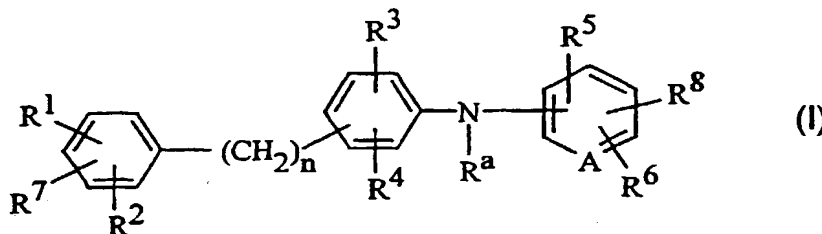
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF INHIBITING AMYLOID PROTEIN AGGREGATION AND IMAGING AMYLOID DEPOSITS



(57) Abstract: The present invention provides a method of treating Alzheimer's disease using a compound of Formula (I). Also provided is a method of inhibiting the aggregation of amyloid proteins using a compound of the Formula (I) and a method of imaging amyloid deposits, as well as new compounds of Formula (I).

Express Mail No. EF378134357US

WO 00/76489 A2

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Citizenship	
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~~Express Mail No. EF378134357US~~Docket No.
5941-01-DRK

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

METHOD OF INHIBITING AMYLOID PROTEIN AGGREGATION AND IMAGING AMYLOID DEPOSITS

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International

Application Number _____

and was amended on _____

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list name and registration number)

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I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

<u>60/138,550</u>	<u>6/10/99</u>
(Application Serial No.)	(Filing Date)
<u> </u>	<u> </u>
(Application Serial No.)	(Filing Date)
<u> </u>	<u> </u>
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

<u>PCT/US00/15071</u>	<u>5/31/00</u>	<u>Pending</u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
<u> </u>	<u> </u>	<u> </u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)
<u> </u>	<u> </u>	<u> </u>
(Application Serial No.)	(Filing Date)	(Status)
		(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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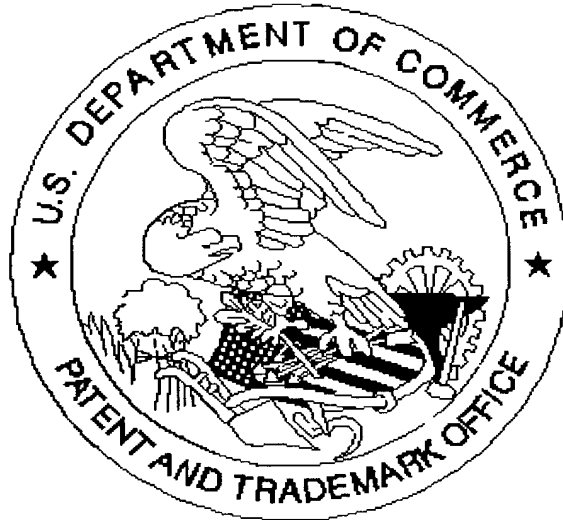
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